Women with an inherited BRCA1 or BRCA2 genetic mutation have among the highest lifetime risks of developing breast and ovarian cancers—many before the age of 50—and as a result often seek information on how to reduce their risk. The options for reducing breast cancer risk for women who have tested positive for mutations in BRCA1/2 genes are few. Currently, women with BRCA mutations can try to manage their increased cancer risk with more intense monitoring (e.g., adding breast MRI to mammograms and breast exams). Alternatively, they can attempt to reduce their risk by (1) having their ovaries and fallopian tubes removed, which lowers the amount of hormones available to stimulate cancer cells and reduces the risk of breast cancer by half (50%) and ovarian cancer by up to 90%; and/or (2) having prophylactic bilateral mastectomy, which reduces the risk of breast cancer by more than 90%. Although reconstructive techniques have improved, surgery is a difficult, invasive, and often unacceptable option for many women.

A novel class of drugs called PARP inhibitors hold promise for the treatment and prevention of BRCA-associated cancers. Cells have multiple systems for repairing DNA damage and the mistakes in DNA that are commonly introduced when cells divide. BRCA1 and BRCA2 are critical for one type of DNA repair, and mutations in these genes can lead to the accumulation of mistakes in the DNA and, in some cases, lead to breast cancer. Tumor cells in individuals with BRCA1 or BRCA2 mutations are already hampered in their ability to repair damaged DNA, and thus, rely on back-up DNA repair pathways for survival. PARP inhibitors block the activity of Poly (ADP-Ribose) Polymerase—or PARP, an enzyme involved in a back-up DNA repair pathway—causing the tumor cells to accumulate so many mistakes in the DNA that they must self-destruct. Since normal cells are not affected by PARP inhibitors, the hope is that these drugs will be a safe and effective way to reduce breast cancer risk or delay breast cancer in high-risk individuals with BRCA1/2 mutations.

This Susan G. Komen for the Cure® Promise Grant supports a promising five-year, $5 million research project to evaluate PARP inhibitors as a novel non-surgical option for preventing invasive breast cancer in women with hereditary BRCA mutations.

**BRCA1- and BRCA2-deficient cells are extremely sensitive to PARP inhibitors.** Normal cells have several systems to repair mistakes in DNA, so blocking the PARP-mediated DNA repair pathway does not affect them. However, DNA repair pathways are already impaired in cells carrying BRCA1 and BRCA2 mutations, and as a result PARP inhibitors cause these cells to die. In essence, mutations in BRCA1 and BRCA2 that can lead to breast cancer, can also be the cancer’s Achilles heel.

Illustration courtesy of Dr. Kornelia Polyak
THE RESEARCH TEAM

Judy Garber, MD, MPH, Director of the Cancer Genetics and Prevention Program at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School and Dana-Farber Cancer Institute, Boston, MA.

Kornelia Polyak, MD, PhD, Associate Professor of Medicine at Harvard Medical School and Dana-Farber Cancer Institute, Boston, MA.

Drs. Garber and Polyak, Promise Grant Co-Principal Investigators, have assembled a unique team of investigators—experts in breast cancer initiation and progression, cancer genetics, breast cancer risk assessment, pharmacogenetics, the tumor microenvironment and stem cells, chemoprevention clinical trials, and biomarker development. In addition to Harvard Medical School and Dana-Farber Cancer Institute, this collaborative, multi-institutional team includes researchers from the University of Michigan, the University of Pennsylvania, Dartmouth Medical School, and Duke University School of Medicine, among others. Together with a team of patient advocates that will help raise awareness about the clinical trial, contribute to protocol development, and monitor its progress and safety, they are working to develop a new strategy for preventing breast cancer in women at highest risk. In addition, the team has assembled a panel of internal advisors and a Data Safety Monitoring Committee to help monitor and focus its efforts to improve prevention options for women who are BRCA1/2 mutation carriers.

THE RESEARCH PROJECT AND GOALS

The research funded by this Promise Grant is studying a novel class of drugs—PARP inhibitors—as potential breast cancer chemopreventive agents for BRCA1/2 mutation carriers. Because PARP inhibitors are still a relatively new weapon in the arsenal against cancer, further information is needed about their safety and effectiveness and the underlying biology, before they can be offered as a medication used for breast cancer prevention. Specifically, the project has five integrated goals:

1. Study the effectiveness of multiple oral PARP inhibitors as chemopreventive drugs in an animal model of breast cancer caused by BRCA1 mutation. These preclinical (laboratory) studies will determine which of these drugs can best reduce the development of tumors in mice, examine the drugs’ side effects, and help determine the lowest dose of oral PARP inhibitor that could be used to prevent tumor formation in mice. In addition, the team will conduct preclinical studies:
   • to explore possible biomarkers that could help monitor a patient’s response to the drug,
   • to evaluate a high-dose, intermittent chemoprevention strategy (rather than long-term consistent use), and
   • to test an oral PARP inhibitor in combination with other promising prevention drugs.

   All of these studies will provide important information about the safety and efficacy of oral PARP inhibitors as chemoprevention drugs that will inform the clinical trial.

2. Conduct an early (Phase I) brief exposure clinical trial of an oral PARP inhibitor in healthy women who are high risk due to inherited BRCA mutations and are planning to have
a prophylactic bilateral mastectomy. This multi-institutional clinical trial, which is the first of its kind, will identify the lowest effective dose of an oral PARP inhibitor as a breast cancer chemopreventive agent and provide important information that could lead to a large, definitive cancer prevention trial using a PARP inhibitor. Blood and breast tissue samples collected during the trial will be used to evaluate and develop biomarkers as described below.

3. Determine the effect of an oral PARP inhibitor on human breast cancer stem cells and early progenitor cells in BRCA mutation carriers by looking at how the drug affects the cells’ numbers and their ability to self-renew and whether the drug induces apoptosis (cell death) in these cell populations. These studies will provide insight into how PARP inhibitors work (the researchers believe these drugs exert their cancer preventative effects by altering the number or function of breast cancer stem cells or progenitor cells), and provide the basis for developing biomarkers to monitor response to the drug.

4. Define the molecular signatures of human mammary epithelial cells in BRCA1 and BRCA2 mutation carriers before and after exposure to an oral PARP inhibitor. These studies will look for the effects of the PARP inhibitor on important genes and proteins in the breast tissue and breast stem cells, and help identify biomarkers that are associated with a response to the drug.

5. Adapt biomarker assays for use with the smaller tissue samples collected through random periareolar fine needle aspiration (RPFNA), a technique for serially sampling breast cells from high-risk women. These assays could be used to monitor women in a larger prevention trial to rapidly tell if the medication was hitting its target.

**HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?**

Almost 200,000 individuals have had BRCA testing, and more than 40,000 mutation carriers have been identified. Women often learn they are carrying a mutation in their 20s or 30s, and then must cope with a lifetime breast cancer risk of 50-85%, as well as a markedly elevated ovarian cancer risk. Most of these mutations have been passed down for generations and will burden the daughters and granddaughters of women and men whose mutations are identified today. There are few options available to reduce their risk, and the most effective of them are surgical procedures that may be unacceptable to many in this very high-risk population.

The multi-disciplinary research team funded by this Promise Grant is collectively focused on the goal of evaluating the role of PARP inhibitors in breast cancer prevention. If successful, these studies will provide information that could lead to a large, definitive cancer prevention trial with a PARP inhibitor for women with BRCA mutations. A safe, effective oral agent that could prevent or significantly delay breast (and ovarian) cancer in thousands of young, healthy women and their descendents would comprise an exciting option for nonsurgical cancer prevention that could fundamentally change the burden of a BRCA1/2 mutation.

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**Cancer preventative approaches for BRCA1/2 mutation carriers are currently limited to increased surveillance and prophylactic mastectomy. We will assess if short-term use of PARP inhibitors could be used for cancer prevention in these patients**

— Judy Garber