FOCUS on Prevention

Over the past 10 years, a decided shift has occurred in recognition of, and funding for, the concept of breast cancer "prevention." From its first grant awards in 1982 through 2010, Susan G. Komen for the Cure's investment in research focusing on prevention of breast cancer has increased almost three-fold. For scientists and advocates, this change reflects a true "paradigm shift."

In his influential book "The Structure of Scientific Revolutions" (1962), Thomas Kuhn described the concept of "paradigm shift." While used today to describe any profound change, Kuhn developed this phrase specifically to "describe a change in basic assumptions within the ruling theory of science." Kuhn further details this phenomenon as the result of a "scientific revolution" that occurs when previously held tenets, often universally accepted, fail to explain anomalies discovered either by scientific experimentation or simply by observation. As these contradictions accumulate, science appreciates that a crisis exists and begins to explore alternatives to the long-standing, obvious-seeming assumptions that guided previous work, and begins the process of "shifting" to a new paradigm to foster the search for answers to the questions before them. By this very mechanism, and the new frontier being opened by genomics, the long- accepted theory that preventing breast cancer was impossible is now being questioned.

What do we mean by "prevention"?

Komen for the Cure has been at the forefront in funding innovative research related to prevention, addressing the concept of prevention in two ways:

- Preventing (reducing the risk of) breast cancer from **occurring**
  - Vaccine development
  - Cell biology and genetic drivers of cancer
  - Risk reduction strategies (diet, exercise, environmental exposures)
- Preventing (reducing the risk of) **recurrence** of breast cancer
  - Biomarker development and measurement
  - Risk-reduction strategies (diet, exercise, environmental exposures)
  - More effective treatment options

Komen has dedicated nearly $65 million of its research portfolio to prevention research since 1995, the first year a prevention grant was awarded. Komen's commitment to finding ways to prevent breast cancer has continued to grow (Chart A). In the last three years, the organization has invested over $40 million dollars in prevention-related research. The current portfolio includes 59 active prevention research grants (Chart B) exploring a wide variety of potential interventions.

Chart A: Prevention Research Grants Awarded 1982-2010

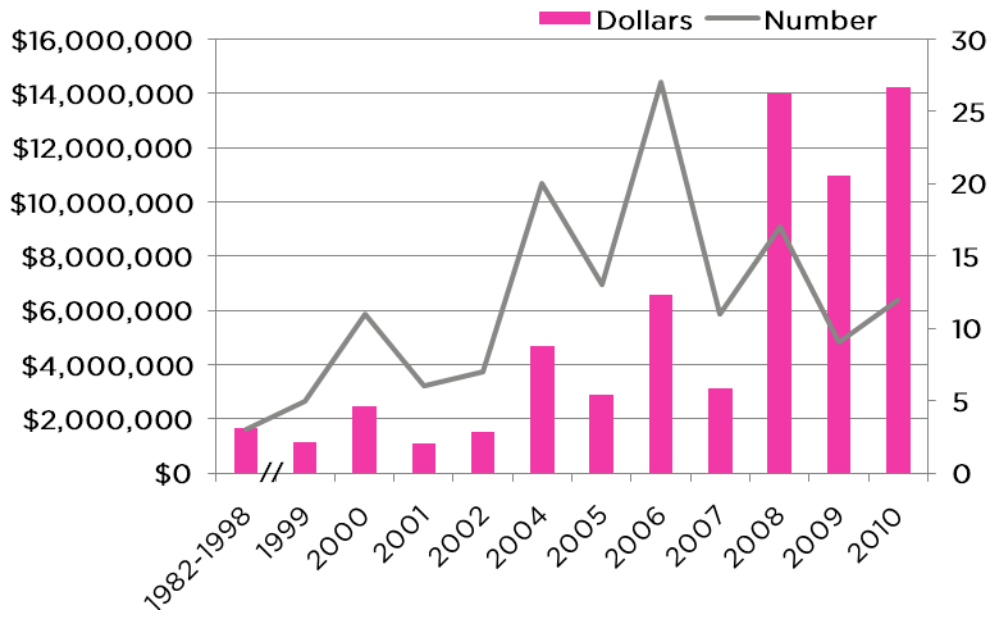
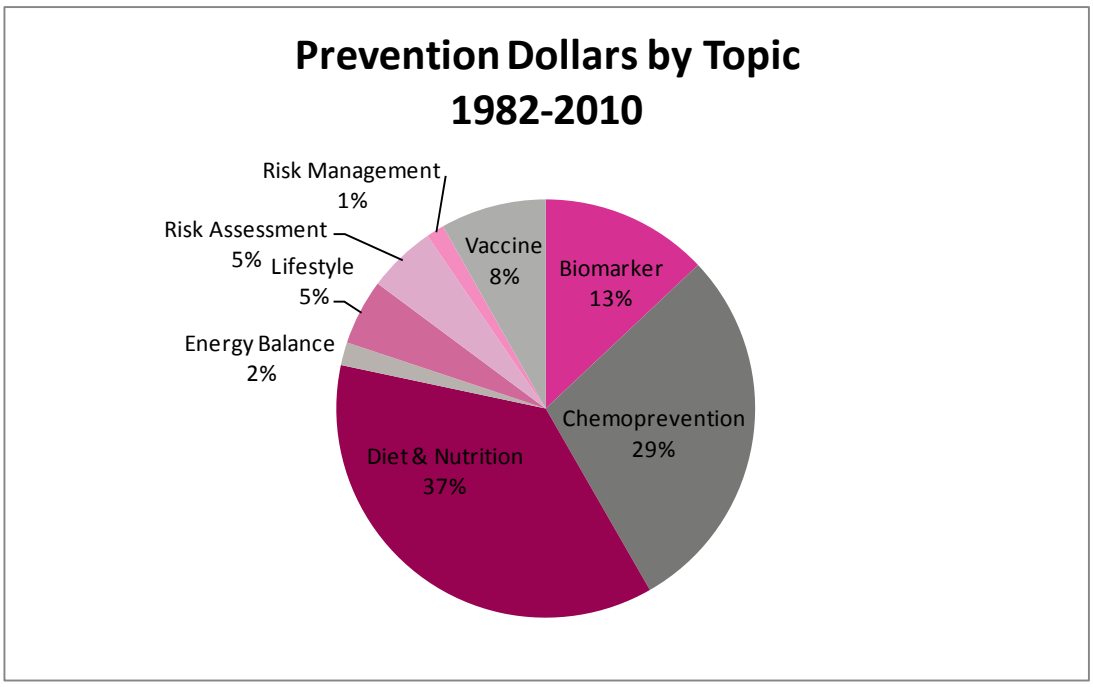


Chart B: Prevention Dollars by Topic 1982-2010



Total Investment in Prevention: $64,372,928

The “Promise” of Prevention

In 2010, Komen’s Scientific Advisory Board emphasized the importance of prevention research to Komen’s overall research strategy by establishing the Prevention Promise Grants. These grants raise the bar by supporting combined pre-clinical and early-phase clinical research studies to test promising interventions with the greatest potential to significantly reduce breast cancer incidence (defined as the prevention of: (1) primary breast cancers in previously asymptomatic women or (2) second primary breast cancers in women with a previous history of cancer). Three grants were awarded through this mechanism, all in the scientific category of chemoprevention:

Using SDG, a lignin found in flaxseed, as a prevention strategy for premenopausal women at high risk for developing breast cancer

Award Amount: $4,500,047
Principal Investigators:
Carol Fabian, M.D.
University of Kansas Medical Center - Kansas City, KS
Stephen Hursting, M.D.,
University of Texas at Austin - Austin, TX

Preclinical evaluation and clinical evaluation of an oral PARP inhibitor for breast cancer prevention in BRCA mutation carriers

Award Amount: $4,999,953
Principal Investigators:
Judy Garber, M.D., Ph.D. & Kornelia Polyak, M.D., Ph.D.
Dana-Farber Cancer Institute - Boston, MA

Chromatin remodeling as a preventive strategy in breast cancer

Award Amount: $500,000
Principal Investigators:
Jose Russo, MD & Irma Russo, M.D.
Fox Chase Cancer Center - Philadelphia, PA

Prevention research is part of Komen’s overall strategy to energize science to find the cures. “Komen’s steadfast commitment to fund research projects in the U.S. and internationally is a critical component in the ongoing effort to treat and eventually prevent breast cancer,” said Eric Winer, M.D., Komen’s chief scientific advisor.

The Advocates in Science Communications Working Group recently conducted interviews with two of the principal investigators, Drs. Fabian and Garber.

Using the lignin, SDG, as a prevention strategy for pre-menopausal women at high risk for developing breast cancer

Will "flaxseed" each day keep breast cancer at bay?

Dr. Carol Fabian and her research team received a Promise Grant for their proposed research to determine if secoisolariciresinol (SDG) – a plant lignin found in high concentration in flaxseed - is likely to prevent premenopausal breast cancer. Their research design consists of: (1) a human trial assessing the effect of SDG on risk markers in benign (non-cancerous) breast tissue of premenopausal women at high risk for developing breast cancer; and (2) a study to determine SDG's effect on risk markers and cancer development in ER+ ("ER positive") and ER- ("ER negative")[1] mice/rat "models" (specifically created by scientists to mimic human breast cancers). This trial is being conducted at the University of Kansas and seven other universities and cancer centers in the United States. A recent visit with Dr. Fabian highlighted her expectations for that research.

What do you hope to accomplish?

Few premenopausal women will agree to take the standard drug tamoxifen, which has been shown to reduce the risk of ER+ breast cancer; and there are no standard medications for reducing ER- breast cancer risk. We hope SDG might present a safe and viable alternative for preventing ER+ and ER- breast cancers.

We anticipate SDG, given in a dose unlikely to cause undesired side effects , or changes in menstrual cycle or fertility indicators, will reduce breast tissue proliferation, as well as precancerous morphologic changes. Since SDG's effects on breast cancer incidence cannot be measured in a trial of this duration and number of participants, parallel studies will be conducted in rats/mice predisposed to breast cancer. These trials will study the effects SDG on prevention of: (1) precancerous changes and high proliferation in benign mammary (breast) tissue; and (2) ER+ and ER- breast cancer. We will also study SDG's effects on protein and gene expression pathways important in breast cancer's development; thus if SDG reduces proliferation and precancerous morphologic changes, we will know how it works. Finally, we will determine if SDG improves breast pain in study participants who present with this symptom.

What do you anticipate the impact to be on breast cancer incidence or mortality?

Over 69,000 of the anticipated cases of breast cancer in the US this year will be women under 55 (SEER estimates). About 30% of these will be hormone receptor negative. The average age of menopause in US women is 54. If SDG were effective in reducing risk by only 20% in premenopausal women, it's reasonable to assume we could prevent about 12,000 women from

[1] Breast cancer isn't just one disease with one type of treatment. It takes many forms, and is generally described based on the presence of the "expression" of three receptors currently known to fuel most breast cancer: estrogen, progesterone and human epidermal growth factor 2 (HER2). http://ww5.komen.org/BreastCancer/FactorsthatAffectTreatmentOptions.html

developing breast cancer each year if SDG is effective in reducing both ER+ and ER- cancer. If it prevents primarily only ER+ breast cancers, then about 9,000 cases would be prevented.

Although tamoxifen reduces breast cancer incidence by up to 50%, few premenopausal women, even those at high risk, will take it given the side effects and lack of a survival advantage. An economical, safe, prevention alternative, available without a prescription, is much more likely to be used by premenopausal women. Unlike tamoxifen, SDG does not result in increased risk of hot-flashes, blood clots or uterine cancer, and is not likely to interfere with future childbearing. The dose of SDG being used (50 mg/day) is available over the counter at a low cost. Thus, SDG could ultimately have a greater impact on reducing breast cancer incidence than tamoxifen because of greater acceptance.

Why do you think this will work?

Pre-clinical and epidemiologic studies suggest SDG reduces breast cancer incidence. "How" is not entirely clear; but it may be due to a reduction in inflammatory molecules called cytokines, a blunting of signaling from the estrogen receptor signaling, as well as an increase in BRCA1 tumor suppressor gene signaling.

We recently conducted a single-arm pilot study in high risk premenopausal women.[2] In this study, taking SDG at 50 mg/day (roughly the equivalent of 25 grams of flaxseed) for 12 months, reduced breast tissue proliferation and precancerous changes in breast tissue sampled by fine needle aspiration. Side effects were minimal.

Why not use just flaxseed?

To reduce the chance of gastro-intestinal side effects that can occur with raw flaxseed, we are using a commercial preparation of SDG (Brevail) instead of raw flaxseed. Further, since SDG content can vary tremendously from batch-to-batch of flaxseed, the commercial preparation will help ensure that all women are ingesting the desired and consistent amount of SDG.

What role do advocates play and what skill sets do you look for in advocates?

Advocates voicing their preference for safe, inexpensive, easy-to-use, natural products for prevention spurred our desire to find such an option. Our Advocate Advisory Board and the participants in the first trial have helped identify trial designs that satisfy scientific requirements and facilitate recruitment, specimen collection, and retention. Moving forward, they will assist with overall and minority recruitment/retention strategies and implementation, among other things. For instance, a member of the Advocate Advisory Board is participating in the regular research team meetings; another one is on the data safety and monitoring committee.

Our advocates have a variety of skill sets and backgrounds. Specifically, we looked for advocates who understand what it means to develop breast cancer, have a scientific background/understanding, and have been active in reviewing scientific research grants. These individuals are helping us focus on the big questions and helping others understand the

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[2] *Fabian CJ, Kimler BF, Zalles CM, Klemp JR, Petroff BK, Khan QJ, Sharma P, Setchell KD, Zhao X, Phillips TA, Metheny T, Hughes JR, Yeh HW, Johnson KA. Reduction in Ki-67 in Benign Breast Tissue of High Risk Women with the Lignan Secoisolariciresinol Diglycoside (SDG). Cancer Prev Res 2010 Aug 19.* [Epub ahead of print]. PMID: 20724470

research plan and questions being addressed. Since this is a prevention study, we also looked for advocates who have not developed cancer but have previously participated in prevention trials.

Dr. Fabian received her M.D. in 1972 from the University of Kansas School of Medicine. She served her internal medicine residency at Wesley Medical Center, Wichita, KS; followed by a fellowship in clinical oncology at the University of Kansas Medical Center where she has led the development of breast cancer centers for both survivorship and prevention. She currently serves as the director of both those centers; chairs the medical center's Cancer Prevention Research Program; and is a Kansas Masonic Research Endowed Chair.

Preclinical and brief exposure early clinical evaluation of an oral PARP inhibitor for breast cancer prevention in BRCA mutation carriers

Can PARP inhibitors effectively prevent breast cancer in women with BRCA mutations?

Dr. Judy Garber and her research team received a Promise Grant for their proposal to evaluate, in the lab and then in a clinical trial, whether brief exposure to an oral PARP (Poly (ADP-ribose) polymerase) inhibitor would reduce breast cancer risk for women with BRCA mutations. Dr. Garber visited with us about her expectations for that research.

What do you hope to accomplish?

The options today for women who have tested positive for mutations in the BRCA1 or BRCA2 genes are few. Women with BRCA mutations now try to manage their increased cancer risk by several different methods: 1) intense monitoring; 2) reducing hormonal stimulation (removing ovaries and fallopian tubes); and 3) prophylactic bilateral mastectomies. Both removal of ovaries and mastectomies have been shown to significantly reduce the risk of breast cancer development. In contrast, monitoring is early detection which does not reduce the risk of tumor development but could reduce mortality. PARP (Poly (ADP-ribose) polymerase) is a protein involved in a number of cellular processes related to mainly DNA repair and programmed cell death.[1] In our working model for PARP inhibitors, women would take a PARP inhibitor for a brief period – say a month – every year or two to eliminate cells that have begun to transform and become malignant cells. This strategy would be unlikely to permanently eliminate the risk of breast cancer, but could help women delay their breast cancers or need for risk-reducing surgery -- for years, and even forever.

In this first trial using a PARP inhibitor in healthy women who have a BRCA1/2 mutation, we hope to provide information that could lead to a large, definitive cancer prevention trial using a PARP inhibitor. The goal of a larger trial would be to establish a safe, nonsurgical risk-reduction strategy for women at high risk for breast cancer. The very nature of a PARP inhibitor -- one that kills tumor cells without damaging normal cells --would make it a good drug for prevention and treatment.

What do you anticipate the impact to be on breast cancer incidence or mortality?

This trial is a first step. We hope to show that the agent is safe, hits its target (inhibits PARP) in blood and tissue, and affects "biomarkers" that can then be evaluated in a larger trial in which the definitive question: "C*an we reduce breast cancer incidence in these very high risk women?"* is explored.

Why do you think this will work?

We have excellent reasons to be optimistic about PARP inhibitors. First, the laboratory data clearly shows PARP inhibitors kill cancer cells in women with a BRCA1 or BRCA2 mutation. Second, we have clinical data that PARP inhibitors kill breast (and ovarian) cancer cells in women with these mutations. Third, the data from studies on mice show PARP inhibitors fed to the mice whose mammary (breast) tissue is missing either one copy of BRCA1 or BRCA2 (like the normal breast tissue of women with BRCA1 or BRCA2 mutations) reliably reduce the development of the mammary tumors that occur in the control group (mice who do not receive a PARP inhibitor). Importantly for a prevention trial, the safety data at the low dose levels at which a prevention agent should operate have been encouraging.

What roles do advocates play and what skills sets do you look for in advocates?

We have three advocates on this project. The first is Sue Friedman, Director of FORCE (Facing Our Risk of Cancer Empowered), one of the leading organizations for women with BRCA1/2 mutations, . Sue will help raise awareness about the trial, which will be conducted at eight centers around the country. She will also serve on the project 's Advisory Committee, which reviews the progress of the project every six months. Elizabeth Frank, an advocate from Dana Farber, sits on the Data Safety Monitoring Committee, a board set up by a clinical trial sponsor to evaluate trial progress, safety data, and significant outcomes according to FDA regulations.[2]. The third advocate, Ruth Fax, has been working with us on the development of the protocol, particularly, but by no means exclusively, on the consent document.

There was some concern about the recent "postponement" of the development of the Astra Zeneca PARP inhibitor, Olaparib, which has also made it necessary for the project to use the Abbott compound, about which there are fewer data available. Is this a problem?

We have all been disappointed – to say the least – about the decision of Astra Zeneca to delay the development of Olaparib for the BRCA1/2 population where the treatment data have been extremely encouraging. The Abbott drug, Veliparib, has also been shown to be effective in the treatment of BRCA1/2-associated breast cancers, though the studies have been in combination with chemotherapy drugs. There are published data showing that Veliparib inhibits PARP in circulating white blood cells and in breast tissue, so it generally hits its target- an important requirement. We don't know that it is necessary for the agent to be the most powerful in the prevention setting – Veliparib may be effective enough and less toxic – like raloxifene compared to tamoxifen in prevention, where raloxifene has been shown to be less effective as a preventive than tamoxifen, but still quite effective, and less toxic.

Dr. Garber received her MD and MPH in 1981 from Yale University School of Medicine. She served her internal medicine residency at Brigham and Women's Hospital (BWH), followed by

fellowships in hematology at BWH, medical oncology at Dana –Farber Cancer Institute (DFCI), and biostatistics at the National Cancer Institute. She joined DFCI as a fellow in 1985, and now works as a medical oncologist and clinical cancer geneticist.

[1] en.wikipedia.org/wiki/Parp
[2] www.ecri.org/patients/references/Pages/Clinical_Trials_Patient_Reference_Guide_Glossary.aspx