PATHWAYS

A Study of Breast Cancer Survivorship

A NEWSLETTER FOR STUDY PARTICIPANTS SUMMER 2024

Genetics and Breast Cancer

On April 25, 2024, Zero Breast Cancer and Kaiser Permanente Northern California Division of Research hosted the webinar "Genetics and Breast Cancer: Learnings from the Pathways Study and Clinical Practice." Pathways researcher Christine Ambrosone, PhD (Roswell Park Comprehensive Cancer Center), spoke about gene/environment interactions and Pathways study research. Medical geneticist Leslie Manace, MD, MPhil (Kaiser Permanente), explained how genetics is used in clinical practice. In this newsletter article, we are providing an overview of their talks. You can also view the recording at zbclink.org/PathwaysWebinars.

Common Genetic Variations and Breast Cancer

Ever wondered why two people with similar lifestyles can have vastly different health outcomes? This question has fascinated scientists for decades, leading to investigations of the relationship between genetic makeup, exposures and behaviors, and cancer risk and outcomes.

Cancer is not a simple disease with one clear cause. It is like a puzzle with many pieces, including genetics, environment, and lifestyle. While we know some things like aging and exposure to certain substances can increase risk, we don't fully understand how all of these pieces fit together.

Genetics plays a big role in cancer risk. You may have heard of certain genes like BRCA1 and BRCA2 that are linked to breast and ovarian cancer. They contain instructions that affect how our cells grow and repair themselves. If these genes have certain changes, it can strongly increase the likelihood of getting cancer.

While well-known inherited mutations like BRCA1 and BRCA2 get attention for their significant impact on breast and ovarian cancer risk, research also extends beyond these to uncover lesser-known genetic variants. Genome-wide association studies (GWAS) look at all our DNA for small variations in our genes that are associated with risk of disease or outcomes. These small variations, called single nucleotide polymorphisms (SNPs), can impact how our bodies function by turning genes on or off or changing activity. By studying SNPs, researchers seek to uncover hidden clues about why some people are more prone to cancer and different outcomes.

Unlike traditional genetic analyses that focus on individual genetic variants, polygenic risk scores aggregate hundreds or even thousands of SNPs to provide a comprehensive assessment of an individual's genetic susceptibility to disease and different outcomes. By comparing the collective genetic makeup of individuals with a particular disease or outcome to those without, polygenic risk scores offer a holistic view of genetic predisposition. These scores estimate the cumulative effect of multiple genetic variants on disease risk, providing valuable insights into an individual's overall susceptibility.

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Research shows that common genetic variants increase breast cancer risk when combined with environmental exposures. For example, alcohol can cause breast cancer but most people who drink will not develop the disease. Our genes shape how our bodies respond to carcinogenic exposures, and we are increasingly realizing that our lifestyle habits play a big role in cancer risk in relation to the way our genes are expressed. For example, even moderate physical activity can make a difference lowering cancer risk – we do not have to be athletes to benefit. On the flip side, radiation exposure and obesity are linked to increased cancer risk, along with various hormonal and dietary factors.

The key takeaway from our exploration into genetics and cancer risk is the recognition that genetic susceptibility does not mean that someone will definitely get cancer. Rather, it is influenced by many genetic and environmental factors that can interact with genes to either increase or decrease cancer risk.

Pathways Research Approach and Findings

Rather than focus on breast cancer risk, Pathways Study research is about the length and quality of survivorship in people who have had a breast cancer diagnosis. The Pathways Study researchers have leveraged GWAS and polygenic risk scores to explore various health outcomes. For example, collaborators working with Pathways Study data calculated polygenic risk scores for bone density and examined their association with fracture risk in women undergoing treatment with aromatase inhibitors. Aromatase inhibitors are commonly used in the treatment of hormone receptor-positive breast cancer and are associated with an increased risk of bone loss and osteoporosis. They found genetic estimates of bone density predicted fracture risk, shedding light on the potential role of genetics to anticipate and avoid unwanted treatment side effects.

In another study, genetically predicted metabolic traits were investigated in relation to breast cancer outcomes. Although these traits were not directly measured, polygenic risk scores for cardiovascular disease and vascular disease were associated with breast cancer outcomes in participants of the Pathway Study.

Polygenic risk scores are potentially powerful tools in predicting disease outcome risk and informing personalized treatment approaches. Although these findings are intriguing, they are also preliminary and not yet used in clinical practice. As we continue to unravel the intricate interplay between genetics and disease, polygenic risk scores offer a promising avenue for advancing our understanding and improving patient care.

Genetics and Clinical Practice

In clinical practice, next generation technology has taken geneticists from analyzing one gene at a time to looking at hundreds or even thousands of genes in one test. In the past, physicians would wait for symptoms to detect diseases. More recently they use genetic testing to better define someone's risk to inform decisions about screening and treatment and, ideally, to prevent illness and disease.

About 80-85% of breast cancer cases are due to multiple accumulating factors where environment and lifestyle especially matter, but about 10-15% are cases with a hereditary genetic mutation, including hereditary breast and ovarian cancer syndrome (linked to the gene BRCA1, BRCA2), Lynch Syndrome, and more newly recognized genes PALB2, CHEK2, ATM, and more. People born with these known genetic mutations are at higher risk, which varies depending on specific mutation and gene. People who have an extensive family history of breast and other cancers, especially when affecting relatives at young ages, are more likely to have an inherited genetic mutation.

Who Is at Higher Genetic Risk?

People may be at higher risk of hereditary breast cancer if they have any of the following:

- A first-degree relative (mother, daughter, or sister) with breast or ovarian cancer
- A second-degree relative (aunt, niece, grandmother, or granddaughter) with breast cancer before age 50 or ovarian cancer at any age
- A first-degree relative who tested positive for a breast cancer gene
- Male breast cancer in the family

If you or your family members may be at increased risk, talk to your doctor about whether genetic counseling or testing may be an option for you or them.

Genetic Counseling

Genetic counselors are healthcare professionals who help people understand how their genetic information may impact their health together with physician medical geneticists. They do the following:

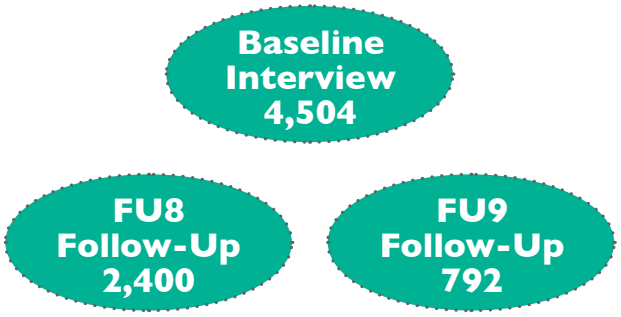
- Complete a detailed review of your medical records, health history and family history of cancer
- Help you understand your chance of developing cancer based on hereditary factors
- Discuss and offer genetic tests that might be right for you or your family
- Order a genetic test, when appropriate, and discuss what results may mean and how that information may be added into your personalized health plan
- Help you understand screening or treatment options personalized based on your personal and family cancer history and/or genetic testing results
- Address your questions and concerns

Getting Support

There are support groups available for people at higher genetic risk that you or your family members might be interested in outside of Kaiser Permanente.

- Facing Our Risk Empowered (FORCE): facingourrisk.org
- Bright Pink: brightpink.org
- Bay Area Cancer Connections: bayareacancer.org
- AliveAndKickn: aliveandkickn.org
- Bay Area Young Survivors: baysnet.org

Pathways Update – Who Is Participating?



We are grateful for your role in Pathways. All of you add meaning and diversity to our team and contribute your unique perspective to the information we are gathering. Thank you for continuing to participate!

For the most up to date information on the Pathways study, please visit our website: http://pathways.kaiser.org

New Contact Information?

In order to keep in touch with you we must have your latest contact information. Please let us know if your phone number or home address has changed. You can reach us by calling our toll-free number: **1-866-206-2979** or email us at dor-pathways@kp.org.

Please note we have moved

The Division of Research moved from downtown Oakland to Pleasanton, as of April 29th, 2024. The new address of the Pathways Study is:

Pathways Study
Kaiser Permanente
Division of Research
4480 Hacienda Dr.
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