Pink ***Team***

The Role of Genetics in Breast Cancer

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Abstract

BRCA 1 and 2 are the two genes that are most commonly linked to breast cancer risk. These genes are present within everyone. Inherited mutations in either or both of these genes can increase an individual's risk to this disease. The aim of this project was to gather information about the extent to which mutations in the BRCA 1 and 2 genes affect an individual's susceptibility to breast and other related cancers, as well as the variability in ethnic distribution of this disease. In order to conduct this research, a variety of resources were used, including the [12]. Komen Foundation website, the Research Gate and Mayo Clinic Databases, and the National Center for Biotechnology Information. Our research showed that BRCA mutations were most prevalent in families that had a strong history of breast and ovarian cancer, suggesting that there was a significant correlation.

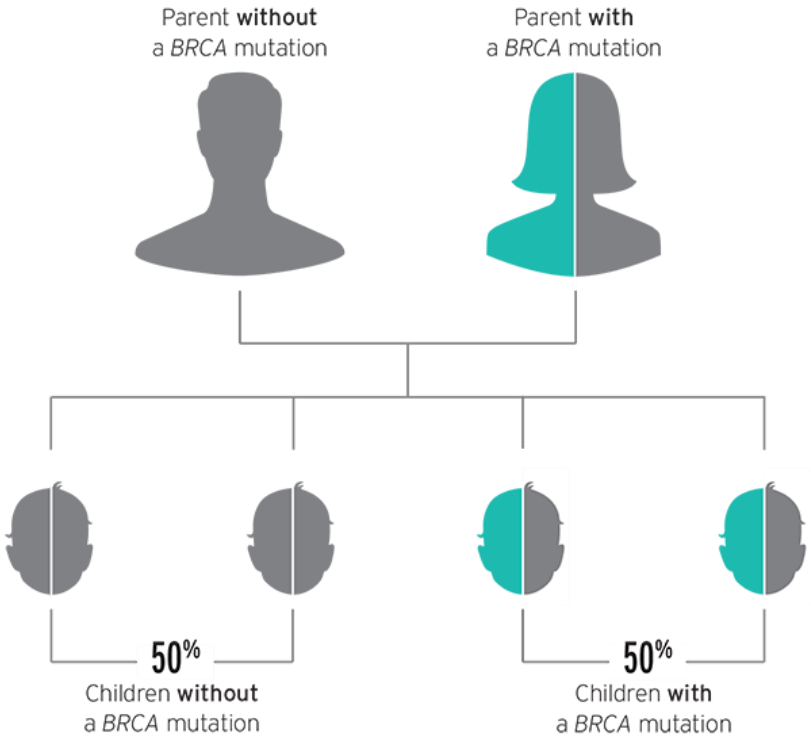
BRCA Mutations

- BRCA (Breast Cancer Gene) 1 and 2 are the genes most commonly linked to breast cancer risk. They are present within anyone, and **mutations** can be inherited from either parent. Mutations in BRCA 1 and 2 can increase an individual's risk of getting breast cancer by 60%.

- BRCA 1: 57-65% probability of breast cancer, 39-40% of ovarian cancer [1].
- BRCA 2: 45-49% probability of breast cancer, 11-18% of ovarian cancer [1].

- BRCA 1 and 2 genes code for **tumor suppressor proteins**. They also help repair damaged DNA. When mutations occur, the proteins are shorter and unable to function normally. Broken DNA accumulates in the cells,

How Genetics Works



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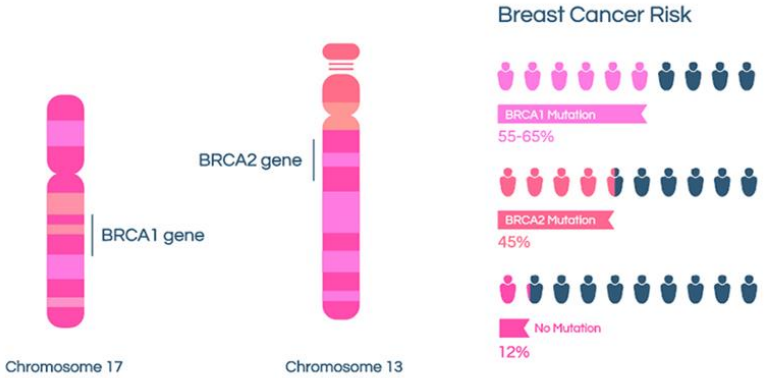

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Genetic Counseling

Talking with a medical expert about the need for BRCA testing based on family history of cancer

Gene Testing

Medical procedure used to check for the presence of a BRCA 1 or 2 mutation

Preventive Measures

Include enhanced screening, Chemoprevention, preventive surgeries such as Mastectomies to reduce risk of developing Breast or Ovarian cancer later in life.

BRCA Gene Counseling

- Genetic counseling is a communication process where a patient worried about their genetic risk of a disease discusses their personal and family medical history with a health professional [2].

- Genetic counseling is usually recommended before genetic testing, as it covers several aspects of the testing process and is a key part to the **informed consent** process [2].

- Counseling can help one figure out whether genetic testing would be appropriate, as well as the implications of certain testing results if they do get tested [2].

BRCA Gene Test

- The BRCA Gene Test uses DNA analysis from the blood to identify the harmful mutations in either of the two breast cancer susceptibility genes. (Ranges from 21,000 to 357,500 Rupees -- around 300-5000 Dollars) [3].
- Interpreting the Results
  - **Positive**: Indicates that the patient has a mutation in one of the two genes, but will not definitely develop Breast Cancer [3].
  - **Negative**: Can be interpreted in one of two ways, true negative or unclear [3].
  - **Ambiguous**: A genetic test finds a change in BRCA1 or BRCA2 that has not been previously associated with cancer [3].
- In order to reduce a patient's risk following genetic testing, doctors may provide options including increased surveillance and enhanced screening, oral contraceptives, **chemoprevention**, or preventive surgery [3].

PARP Inhibitor Therapy

- PARP inhibitors are a new form of treatment for cancers due to mutations, especially Breast and Ovarian cancer [4].
- Poly-ADP Ribose Polymerase (PARP) helps repair damaged DNA in cancer cells. Mutations in the BRCA genes already result in slow and poor repair of cells. By blocking the PARP from doing its work, the cancer cells eventually die off and the healthy cells with proper DNA are spared [4].
- PARP Inhibitors known as *Lymparza* and *Talzenna* have received approval from the FDA as a targeted therapy for **Metastatic Breast Cancer** [4].
- PARP Inhibitors can also be used for **Maintenance Therapy**, to keep the cancer from returning after standard treatment has been completed [5].
- The cost for PARP Inhibitor therapy is between 16,000 and 19,000 dollars, or 10 Lakhs [5].

Link to Prostate and Pancreatic Cancer

- BRCA mutations increase the risk of developing several cancers other than breast [7].
  - In men, BRCA mutations increase the risk of prostate and pancreatic cancer, but other associations may be playing a role as well [7].
- Pancreatic cancer is the 3rd most common cancer to be associated with BRCA 1/2 mutations. Carriers of the BRCA 2 mutation are more likely to develop pancreatic cancer [6].
- Men who possess the BRCA 2 mutation are up to seven times more likely to develop prostate cancer [6].

Link to Ovarian Cancer

- Similar to breast cancer, BRCA1 mutations significantly increase the risk of developing ovarian cancer from 1.3% to 44% [7].
- Although the risk of developing ovarian cancer is higher with a BRCA 1/2 carriers, the survival of patients with BRCA 1/2 seems to be better than non-carriers [12].
    - A possible reason for the improved survival may be the better response to chemotherapy by BRCA carriers. [12]
- Research pertaining to the better survival of BRCA carriers with ovarian cancer is limited and long-term survival is uncertain [12].
- BRCA 1 mutations are more likely to result in ovarian cancer, however, BRCA 2 mutations increase the risk of several other cancers [7].

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- HBOC is an inherited genetic condition, passed down through generations
- Chances that HBOC is present within a family are increased when
  - Breast and/or Ovarian Cancer is present in multiple cases on the same side of the family [9]
  - A male relative is diagnosed [9]
  - A patient is of Ashkenazi Jew ancestry [9]
  - There is familial history of prostate, melanoma, or pancreatic cancer [9]
- HBOC has an autosomal dominant inheritance pattern [9]
- Aside from the BRCA gene, this disease can also be inherited from mutations in TP53, PTEN, ATM, or CHEK2 [9].
  - The PTEN gene is one of the more dangerous inherited genes because it causes Cowden Syndrome, causes people to get cancerous and non-cancerous tumor growth in the Breast, Ovaries, and other areas [9]

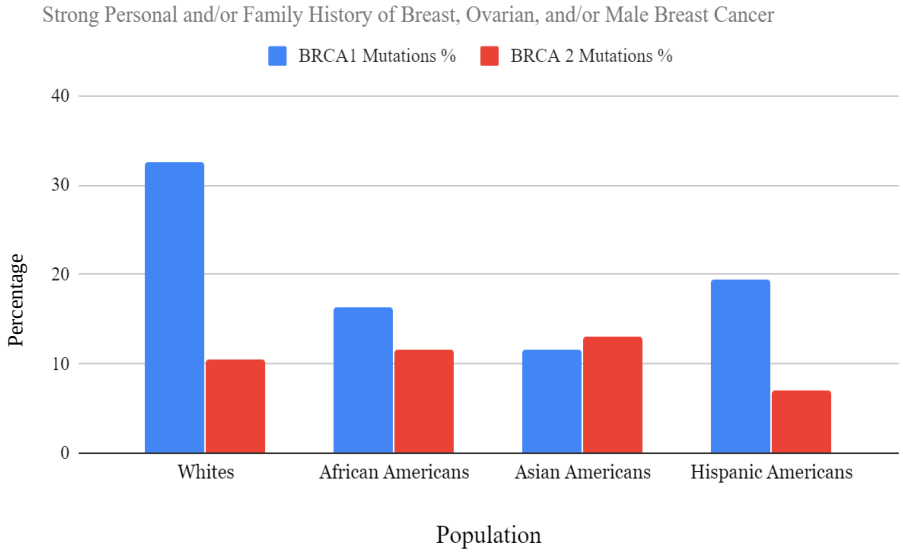
Hereditary Breast and Ovarian Cancer (HBOC) cont.

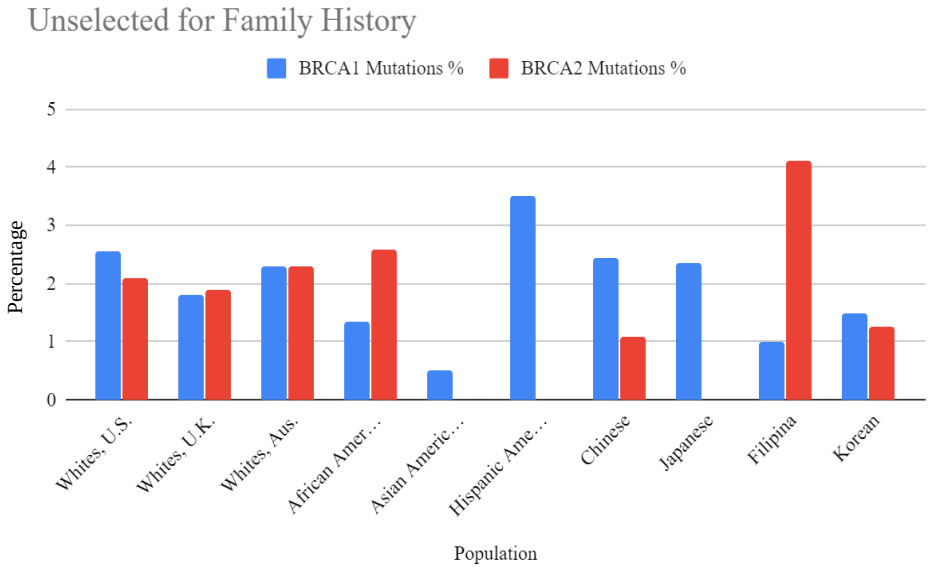
- Prevention Methods [8]
  - **Risk Reducing Oophorectomy:** Preventive surgery, associated with 72% risk reduction in breast cancer.
  - **Tamoxifen Prophylaxis:** reported 49% risk reduction, reduces the occurrence of contralateral endpoints, more effective in younger population (find if it is given to all BRCA patients or only estrogen receptor + patients)
  - **Early Detection:** regular screenings and MRI examinations beginning at a young age, in a family with HBOC mutations.
- In order to reduce a child's risk to inheriting the condition, a Preimplantation Genetic Diagnosis can be performed, along with an In Vitro Fertilization [8]

BRCA, Ethnicity and Prevalence

- In a study of people with strong personal or familial ties to breast or ovarian cancer, the BRCA1 and BRCA2 genes were found to be most prevalent in Whites and Asian-Americans respectively [10].
- In a study of the general population, Ashkenazi Jews had the highest percentage of BRCA1 and BRCA2 mutations, indicating that Ashkenazi Jews could have stronger genetic ties to BRCA mutations than other ethnicities [10].
- In a study of U.S. women with breast cancer, Ashkenazi Jews also had the highest prevalence of BRCA mutations, further revealing that Ashkenazi Jews have stronger genetic ties to the mutations [12].

BRCA, Ethnicity and Prevalence





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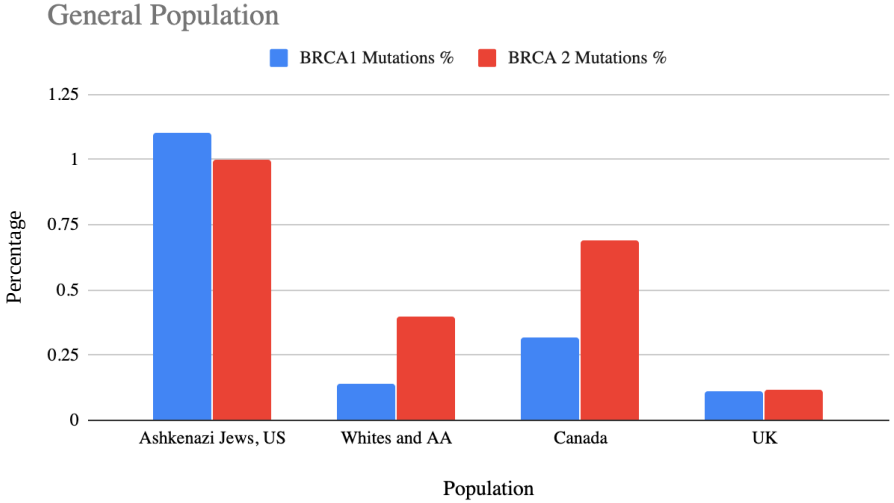
BRCA, Ethnicity and Prevalence



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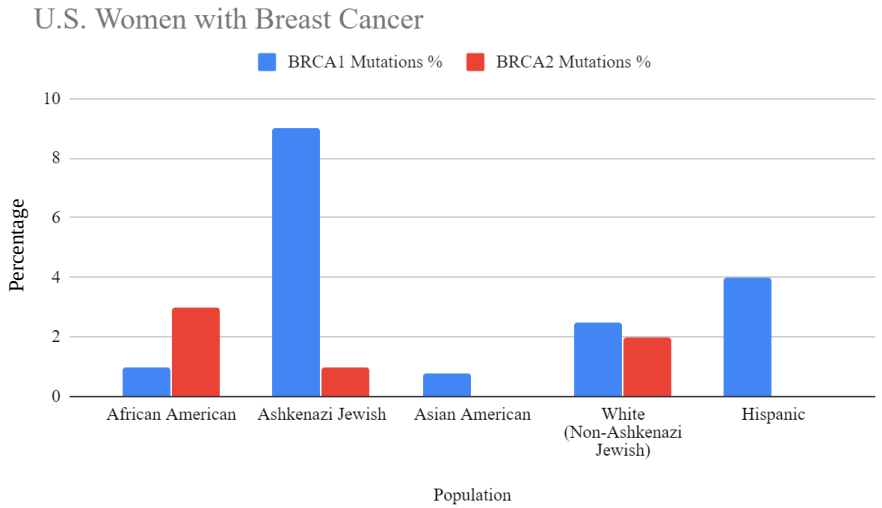

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Debjani's Story

Debjani Saha is a BRCA Mutation carrier who was diagnosed with Triple Negative Breast Cancer at Early Stage II in 2016. She underwent surgery within a week after finding a lump in her breast when she was 29. Though she encountered many setbacks, her willpower remained strong. Now, she is a cancer counselor who helps others going through journeys similar to hers. Today, she continues to motivate everyone around her.

Glossary

- **Mutation:** The changing of the structure of a gene, resulting in a variant that may be transmitted to subsequent generations
- **Informed Consent:** a process in which patients are given important information about a medical test/procedure to help them decide if they want to be tested/treated
- **Chemoprevention:** The use of chemical agents to prevent or slow the development of cancer
- **Metastatic Breast Cancer:** a stage of breast cancer where the disease has spread to distant sites beyond the axillary lymph nodes
- **Maintenance Therapy:** designed to help primary treatment succeed, administered to prevent a relapse.
- **Preimplantation Genetic Diagnosis:** a procedure used prior to implantation to help identify genetic defects within embryos. This serves to prevent certain genetic diseases

References

[1]. BRCA1 gene - Genetics Home Reference - NIH. Retrieved from https://ghr.nlm.nih.gov/gene/BRCA1

[2]. Genetic Testing Fact Sheet. Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet#what-is-the-role-of-genetic-counseling-in-genetic-testing-for-a-hereditary-cancer-syndrome

[3]. BRCA Test Results: What Do They Mean? Retrieved from https://www.bebrcaware.com/i-know-my-brca-status/understanding-brca-test-results.html

[4]. (2017, November 13). General cancer information. Retrieved from https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/targeted-cancer-drugs/types/PARP-inhibitors

[5]. Hereditary Cancer. Retrieved from https://www.facingourrisk.org/understanding-brca-and-hboc/information/cancertreatment/parpi/basics/lynparza.php#text

[6]. Cavanagh, H., & Rogers, K. M. A. (2015, August 1). The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521499/

[7]. BRCA Mutations: Cancer Risk and Genetic Testing Fact Sheet. Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#targetText=As a result, cells are,several additional types of cancer.

[8]. Hereditary Breast And Ovarian Cancer. Retrieved from https://www.preventiongenetics.com/About/Resources/disease/HereditaryBreastAndOvarianCancer.php

[9]. (2019, July 2). Hereditary Breast and Ovarian Cancer. Retrieved from https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer

[10]. Kurian, A. W. (2009, October). BRCA1 and BRCA2 mutations across race and ethnicity: Distribution and clinical implications. Retrieved from https://www.researchgate.net/publication/38022627_BRCA1_and_BRCA2_mutations_across_race_and_ethnicity_Distribution_and_clinical_implications

[11]. Temkin, S. M., & Dizon, D. (2018, July). PARP Inhibitors for Ovarian Cancer: Who and When, And Can We Afford It? Retrieved from https://www.managedhealthcareconnect.com/article/parp-inhibitors-ovarian-cancer-who-and-when-and-can-we-afford-it#targetText=At the recommended dose for,month in the United States.

[12]. (18AD, December 7). BRCA1 and BRCA2. Retrieved from https://ww5.komen.org/BreastCancer/BRCA1andBRCA2.html

[13] "BRCA Inheritance: Are Your Family Members at Risk?" BeBRCAware, https://www.bebrcaware.com/i-know-my-brca-status/testing-for-family-risk.html.

[14] "마크로젠." Macrogen.com, http://www.macrogen.com/en/business/diagnosis_service1.php.