Hereditary Breast and Ovarian Cancer: BRCA1 Failure and the Effectiveness of PARP Inhibitors

Vanessa Miraj
Stuyvesant High School
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Physiology

- 3-10% of breast or ovarian cancers are considered to be HBOC (occurrences estimated to be 1:300 to 1:800)
- Target tissues include:
  - Breast and ovaries in women
  - Breast and prostate in men
- Symptoms vary depending on which cancer is manifested.
- Breast Cancer (most common manifestation): Change in breast size, lumps in breast tissue and constant pain in the breast or near the armpit, redness of the skin on the breast or nipple and blood stained or clear fluid discharge from the nipple.
- Ovarian Cancer: abdominal pain, increased abdominal size, difficulty eating, and changes in bladder control
- Prostate cancer: frequent urination, weakened urinary stream, blood in urine or semen
- Onset age is usually before 50.

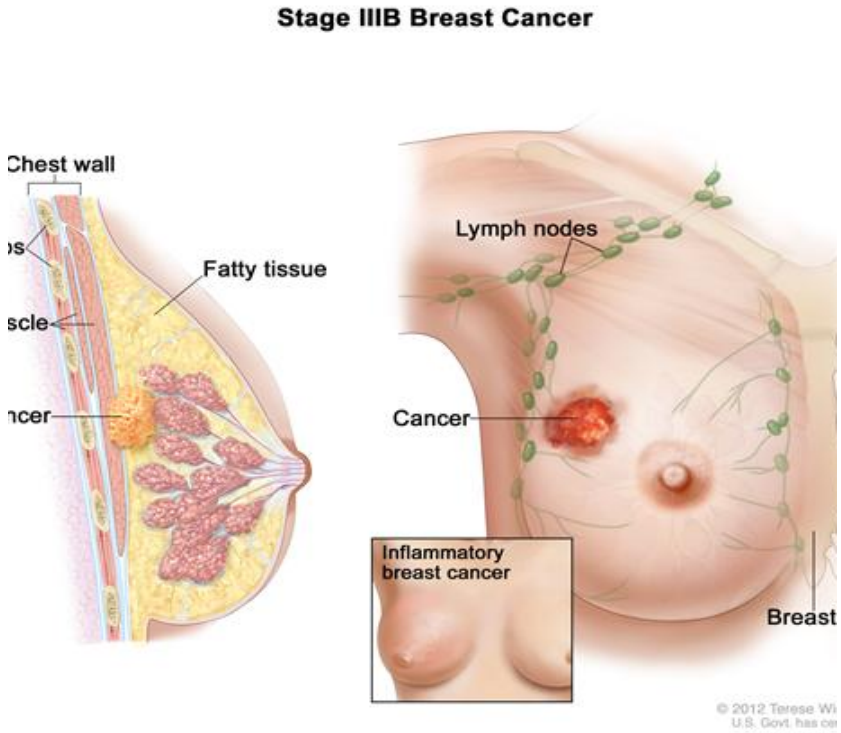
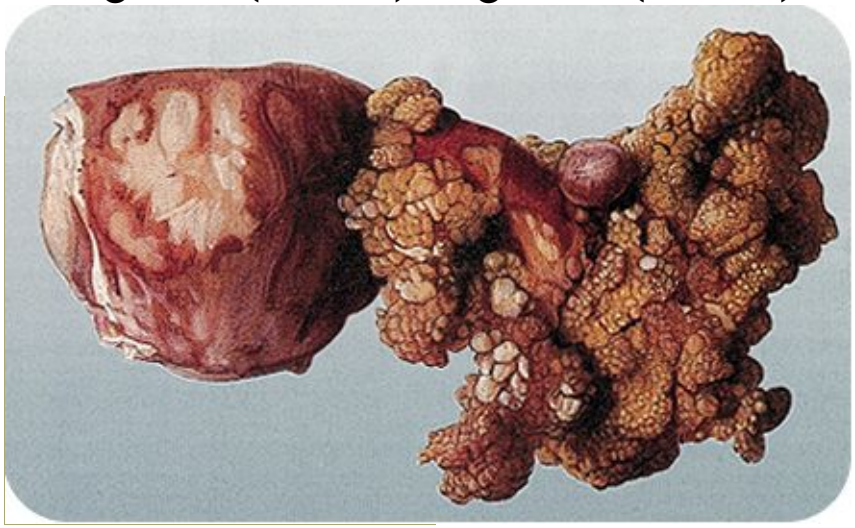
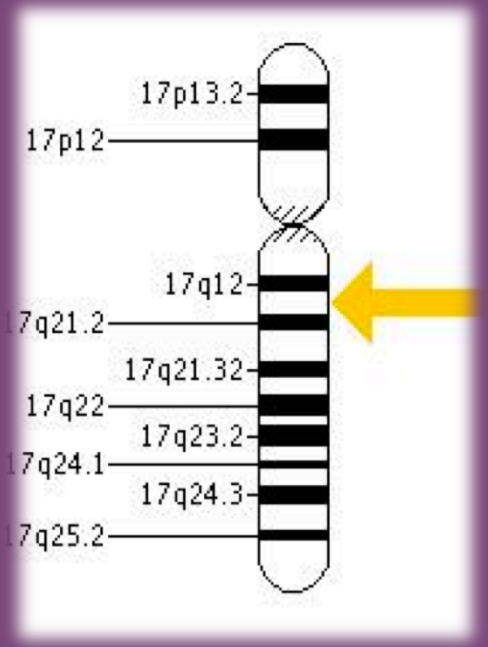


Figure 1(above); Figure 2 (below)

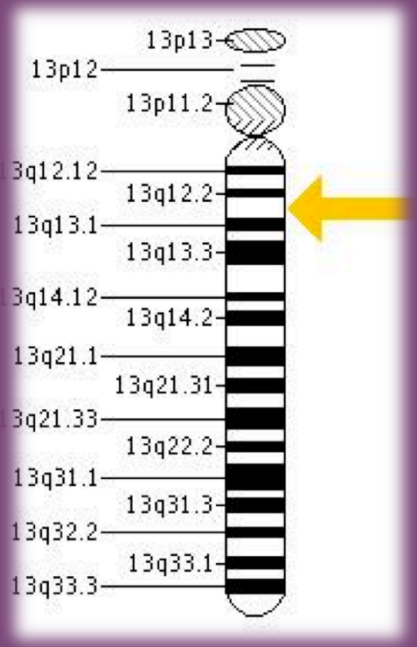


Molecular Cause

- BRCA 1 and BRCA2 belong to a class of genes known as tumor suppressors. If functionally normally they aid in DNA repair
- Transmission: Autosomal Dominant, both are germline mutations, cancer will not actually manifest until both alleles of BRCA1 or BRCA2 lose function, mutation is a deletion starting at promoter.
- BRCA1is located on chromosome 17q21 and BRCA2 is located on chromosome 13q12.
- Interacts with: p53, RB, BRCA2,ATM, RNA polymerase II, PARP1, PARP2, E2F and various other proteins.

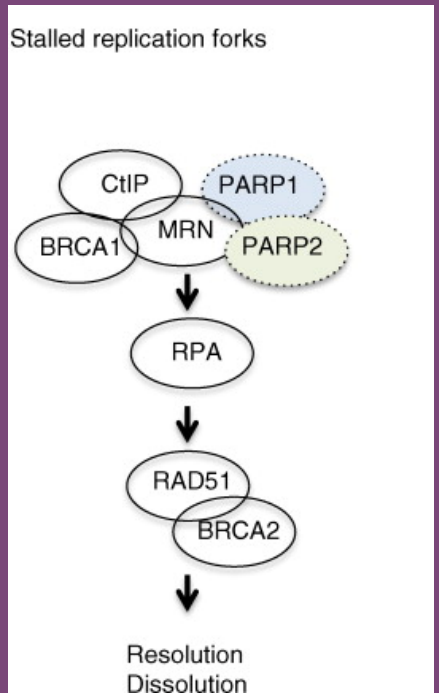


CHROMOSOME 17, Figure 4



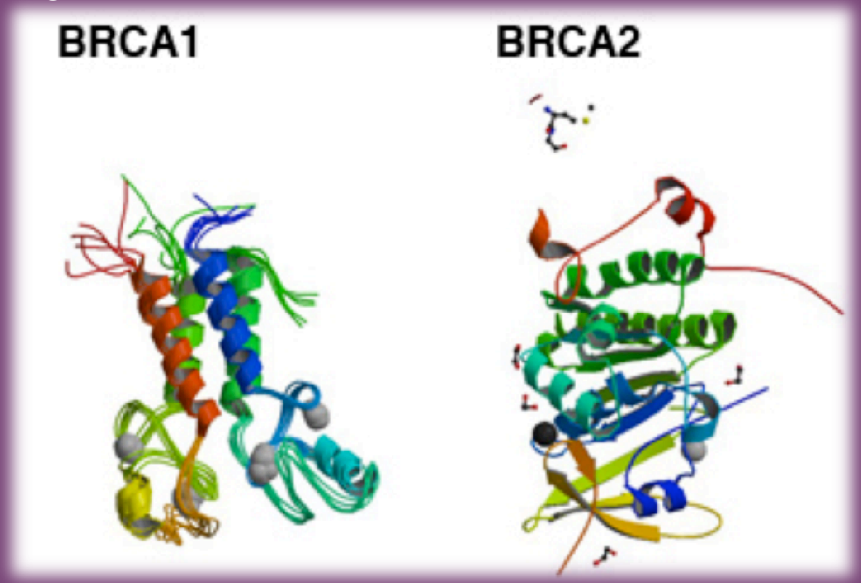
CHROMOSOME 13, Figure 5

Mutations usually lead to a shorter BRCA1 protein or prevent any protein from being made from one copy of the gene. There are over 1000 mutations for this gene. BRCA2 mutations insert or delete a small number of DNA building blocks (nucleotides) in the gene . There are around 800 mutations for this gene



Simplified pathway: The pathway is called the HR pathway which deals with DNA repair. Figure 3

Figure 6



Treatment/Risks and Limits

- Preventative Treatments:
  - Breast Cancer: Mammogram, ultrasounds
  - Ovarian Cancer: pelvic exam and Pap test are used although there is no actual standard for testing
  - Prostate Cancer: prostate examination
- Surgical Treatments
  - Breast Cancer: Bilateral mastectomy or surgical removal of both, lumpectomy or a surgical removal of the cancerous lump in the breast.
  - Ovarian Cancer: hysterectomy, the total removal of the uterus and parts of the ovaries or bilateral Salpingo-oophorectomy, the surgical removal of the ovaries and both fallopian tubes
- Chemotherapy and Radiation Therapy
    - Chemotherapy is used often used to kill cancer cells if the cancer is to big to be removed surgically or after surgery to get rid of any remaining cells. Anthracyclines are drugs that inhibit DNA and RNA synthesis and damage cell membranes, proteins in DNA. They are the most effective anticancer drugs. EX: Adriamycin, Ellence, and Doxil
    - Taxanes are drugs that disrupt microtubule function which are essential to cell division. Ex. Taxotere, Taxol, and Abraxane
  - Radiation therapy kills cancer cells by damaging DNA with high-energy radiation such as gamma rays.

Proposed Cure/Limits

- Researchers at the Netherlands Cancer Institute studied the effects that targeting the Polycomb-group protein EZH2 would have in mice that had a BRCA1 mutation. The results of the study relayed that EZH2 is over expressed in mice mammary tumors. They were also able to see that an increase in EZH2 protein levels is also evident cancer patients with a *BRCA1*-mutation. An inhibitor of EZH2, 3-deazaneplanocin A (DZNep), is around 20-fold more effective in terminating BRCA1-deficient cells.
- Proposal is to use the idea of an inhibitor on a different protein known as PARP1 and deliver it to mice with a BRCA1 mutation. PARP1 proteins replace BRCA1 in DNA repair in cancer cells.
  - PARP inhibitors would stop repairs of the breaks in single DNA strands leading to double strand breaks. In cancer cells the breaks can not be efficiently repaired leading to the death of the cells.
  - Normal cells don't replicate as often as cancer cells and still have an operating homologous repair pathway allowing them to survive with PARP proteins.
  - Delivery would be by injection to breast tissue.
- In theory PARP inhibitors would work with no adverse effects on the rest of the body. However, side effects cannot be known without further research and testing.

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Molecular Cause Slide

Content

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