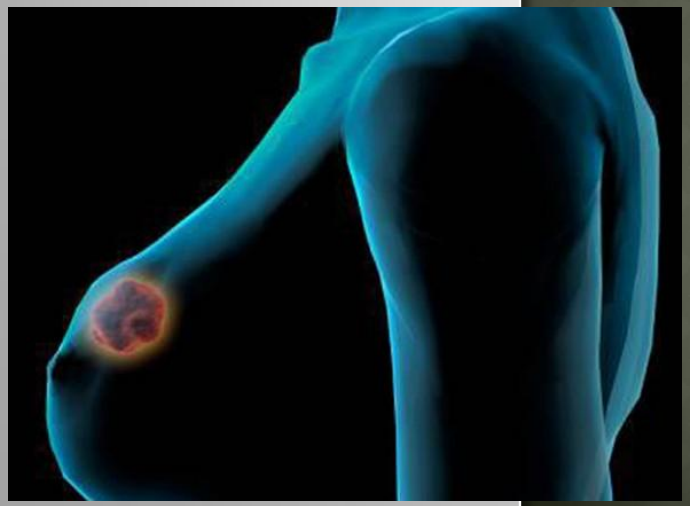
HEREDITARY BREAST AND OVARIAN CANCER: WHEN BRCA1 AND BRCA2 GENES GO WRONG



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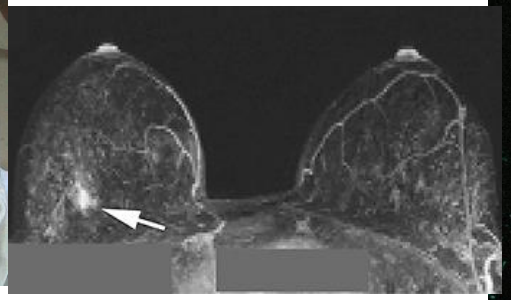
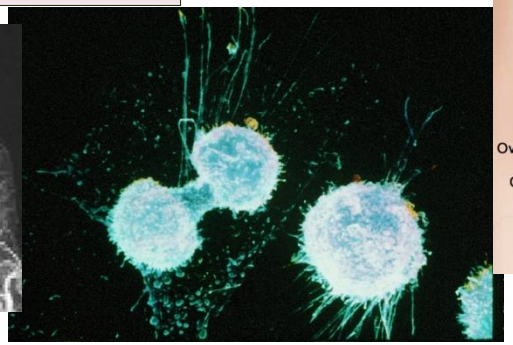
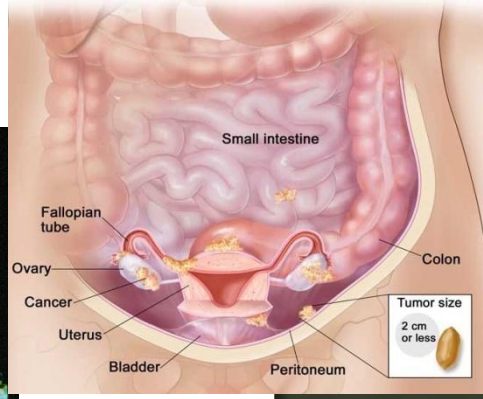
May 20th, 2013

PHYSIOLOGY

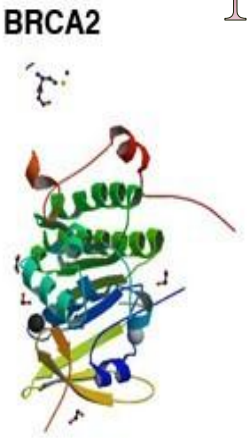


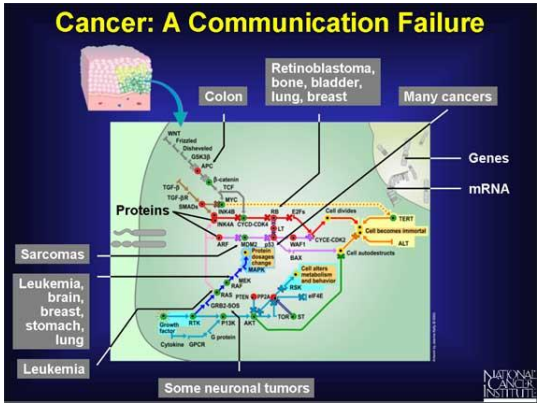


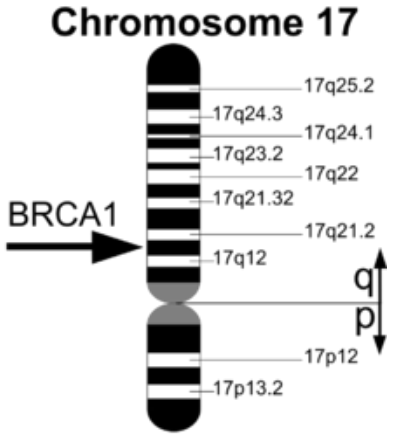


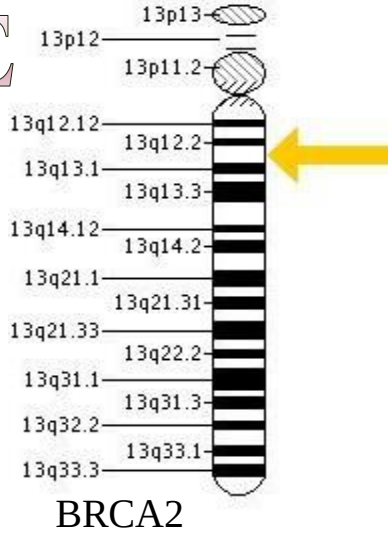
- Of all breast cancers, only 3 – 10% are hereditary
- BRCA mutations are the most common mutations in genes
- Variable expressivity and incomplete penetrance
- Age of onset for females is before 45~ or menopause
- Founder affect in Iceland and among Ashkenazic Jews
- Increased risk for several kinds of cancers, including breast, ovarian, prostate, colon, pancreatic, bile duct, gallbladder
- Cancers are similar to those that occur sporadically
- Symptoms of breast cancer: inverted nipple, nipple discharge, change in color, shape or texture, dimpled skin, pain in the area and increased breast sizes that is unrelated to the menstrual cycle, swelling of lymph nodes around the armpit, or a lump of the breast
- Symptoms of ovarian cancer: pelvic or abdominal pain, bloating, unnatural eating habits (such as getting full quickly), or the need to urinate more than usual
- Ovarian cancers symptoms are harder to detect than those of breast cancer

MOLECULAR CAUSE









- BRCA1 and BRCA2 are tumor suppressor genes in humans
- Autosomal dominant – only one copy of the mutated gene is enough for the disease to manifest
- Most common mutation is the 6174delT on the BRCA2 gene located on chromosome 13 at 13q12.3
- BRCA1 and BRCA2 are responsible for DNA repair, transcriptional activation, and the regulation of the cell cycle
- Loss of function in these genes causes chromosomal instability and mutations in other tumor suppressor genes
- Genetic lesions can be deletions, insertions, or translocations. There's no specific type of mutation since any type of mutation on the tumor suppressor genes will increase the risk of cancer

TREATMENTS/RISKS AND LIMITS

- Since these cancers are similar to those that occur spontaneously, similar therapies are used
- The use of tamoxifen, an estrogen antagonist, in chemotherapy targets estrogen-receptor positive cancers. However, HBOC usually causes cancers that are estrogen-receptor negative so it's not that effective. Side effects: Blood clotting problems like stroke, deep vein thrombosis, and pulmonary embolism, and endometrial cancer
- Reduces breast cancer in women under the age of fifty 49%
- Raloxifene is commonly taken to treat osteoporosis but studies show that it can prevent breast cancer development by blocking estrogen. Side effects: blood clotting in eyes, lungs, or legs and stroke
- Aromatase inhibitors stop the conversion of androgens to estrogen, which can stimulate the growth of breast cancer cells. Tumors need the estrogen to grow and develop. Side effects: blood clot, osteoporosis, and heart problems
- Mastectomy and oophorectomy - the removal of the breast and ovary tissues that have been infected. This approach reduces cancers by 90%. However, some affected tissues often remain and because the cancers are hereditary, they can develop more than once

PROPOSED CURE/LIMITS

- Targeting histone deacetylase (deacetylation is the removal of acetyl groups from the amino acid on a histone)
- DNA expression is regulated by acetylation and deacetylation. Acetylation (which normally occurs) causes amines on the histone to change into amides and decreases the histone's ability to bind to DNA so that transcription can occur.
- Deacetylation allows histones to bind tightly onto DNA. This binding condenses DNA structure and prevents transcription.
- Introduce a liposome filled with these inhibitors which are taken orally. They will follow through epigenetic pathways, which are used for modifying a genome by regulating the gene expression and still keeping the nucleotide sequence unchanged.
- Some achievements already made with this technique: DNA methylation and histone modification (DNA methylation is when you add a methyl group to cytosine or adenine of DNA nucleotides. It's a stable way to alter the expression of genes when they divide and turn into specific tissues)
- The histone deacetylases are involved in pathways where pRb (a retinablastoma protein) suppresses cell growth and division. The pRb attracts these enzymes to the chromatin, which will cause histones to deacetylate.
- Histone deacetylase inhibitors will induce p21 (regulates the cell cycle) expression, which regulates p53's tumor suppressor activities and shift the balance in favor of acetylation so that transcription will take place like it normally should.

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