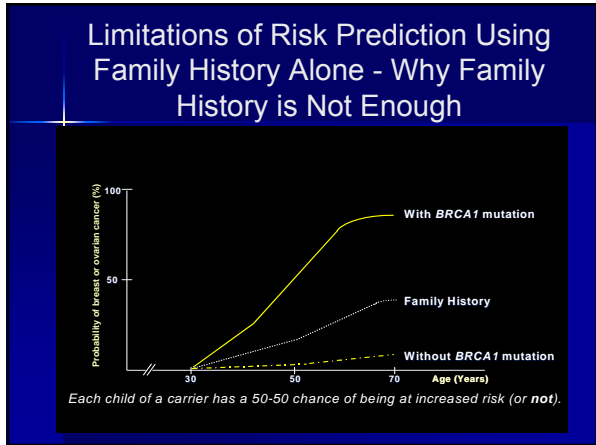
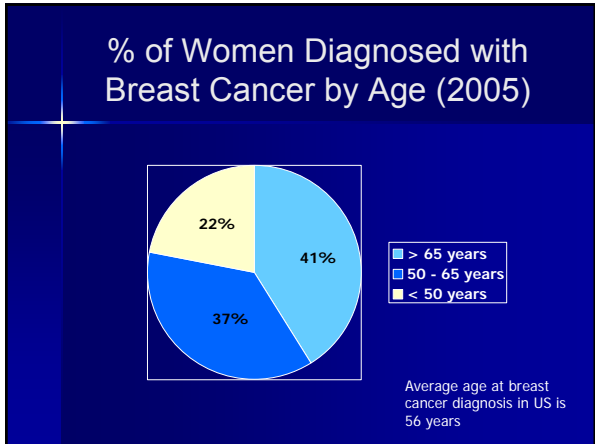


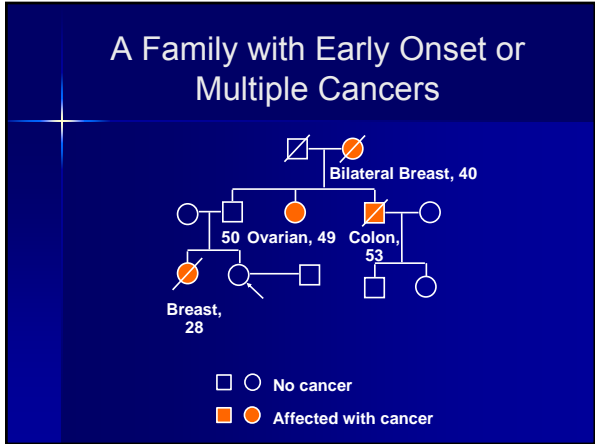
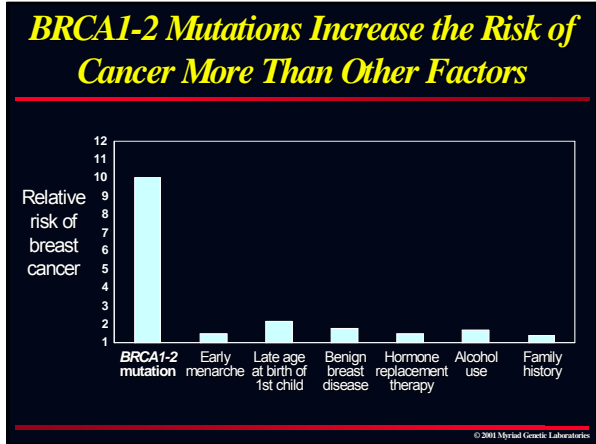
From Research To Action:
 Breaking New Ground
 Symposium

Young Women with Breast Cancer
 Workshop:
 Hereditary Breast Cancer and
 Genomics



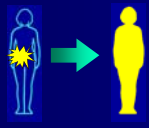
Genetics and Breast Cancer

- For the average woman, the lifetime risk of breast cancer is approximately 11%.
- About 5-10% of breast cancer is caused by a hereditary predisposition



All Cancer Arises from Genetic Mutations

Germline Mutations




All cells affected in offspring

Present in every cell of the body and are inherited from either the egg or the sperm

Inherited

Comprise 5-10% of all cancers

Somatic Mutations



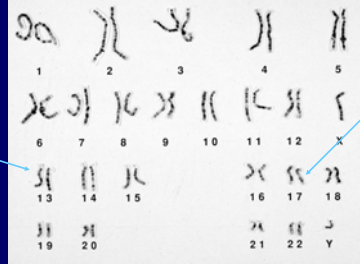
Occur in organs, i.e. the breast

Occur as a result of DNA "damage"

Are not inherited

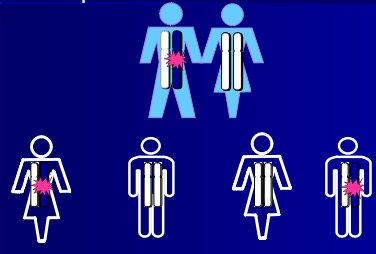
Most cancers develop this way

Chromosomes



BRCA1 BRCA2

Inherited predisposition to cancer can be related to maternal or paternal inheritance



50/50 Rule

What Are the Cancer Risks For BRCA Carriers?

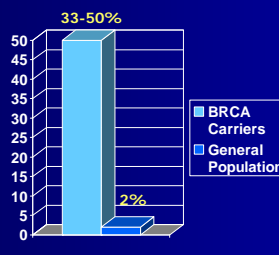
For Women:

- 56-87% lifetime risk of breast cancer
- 25-44% lifetime risk of ovarian cancer

For Men:

- 6% lifetime risk of breast cancer
- Twice as likely to develop prostate cancer
- Six times as likely to develop pancreatic cancer
- Majority of risk is seen in BRCA2 carriers

Breast Cancer Risk In Women < 50 years of age



Group	Breast Cancer Risk (%)
BRCA Carriers	33-50%
General Population	2%

Breast Cancer Risk in Women < 50 years

Inherited versus Acquired Mutations

Sporadic :

2 acquired mutations → Tumor develops

Hereditary:

1 inherited and 1 acquired → Tumor develops

Options for Women At High Risk

Enhanced Screening

- Starting as early as age 25
- Inclusive of screening breast MRI

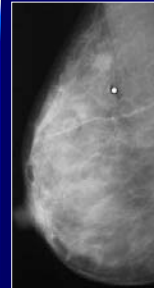
Chemoprevention

- Tamoxifen
- Likely Evista (Raloxifene) in the future

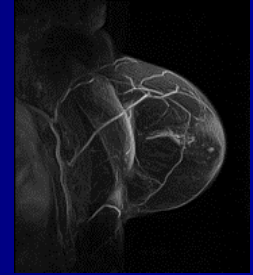
Surgical Risk Reduction

- Prophylactic bilateral mastectomy
- Prophylactic salpingo-oophorectomy

Enhanced Breast Screening



Vs.

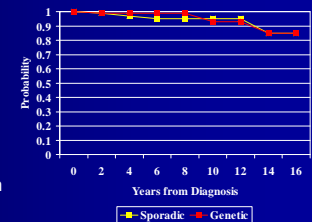


What about Young Women Who Have Already Had Breast Cancer?

- The risk of a second breast cancer is higher in women carriers who have already had breast cancer ~ 60% over a lifetime
- The risk of a subsequent ovarian cancer ~ 12% within 10 years

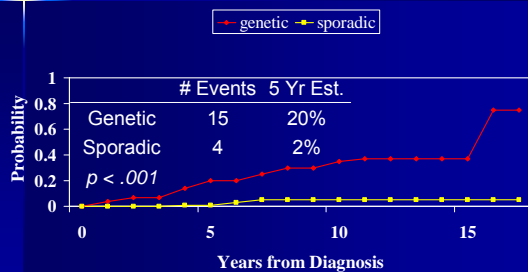
Surgical Options: Breast Conservation

- 71 BRCA (+) ♀ with stage I or II BrCa matched 1:3 with 213 ♀ with sporadic breast cancer.
- No evidence of increased radiation sensitivity of sequelae in breast tissue heterozygous for a BRCA 1/2 germline mutation.



Pierce *et. al.* JCO 2000; 18:3360-3369.

Contralateral Breast Cancer Risk



Pierce *et. al.* JCO 2000; 18:3360-3369.

Prophylactic Mastectomy



Preoperative



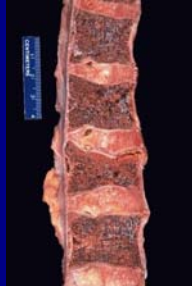
Postoperative

Prophylactic Oophorectomy

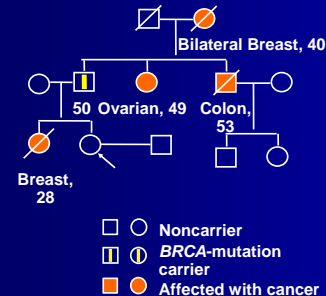
- **HORMONAL ISSUES!**
- **Osteoporosis**

Women who stop producing estrogen due to natural or iatrogenic menopause experience a rapid bone loss.

After bilateral oophorectomy, the loss of trabecular bone has been reported to be as great as 20% during the first 18 months after surgery.



Important to Understand Family History



Family Structure is Important!

- JAMA 2007 Jun 20; 297(23): 2587-95
- 1543 women from a high risk registry were evaluated for risk of BRCA mutation and family structure
- 306 women had developed breast cancer before age 50 and no first- or second-degree relatives with breast or ovarian cancer.
- 13.2% of those who had a limited family structure (fewer than 2 female first or second degree relatives in either lineage) were found to have mutations vs. 5.2% of women with adequate family structure. ($p = 0.02$)

** Those women diagnosed early without a family history should not be eliminated from the option of genetic testing. **

Founder Mutations

There are three common mutations found in individuals of Ashkenazi Jewish descent (about 1 in 44 carry a mutation).

- 185delAG on *BRCA1* is found in 0.8-1.0%
- 5382insC on *BRCA1* is found in 0.15-0.4%
- 6174delT on *BRCA2* is found in 1.2-1.5%

Who may have a hereditary predisposition to breast cancer?

- BRCA mutations are rare in the population (1 in 400-800) but high risk individuals exist
 - Early onset breast cancer (<50)
 - Bilateral breast cancer
 - Women with ovarian cancer
 - Male breast cancer
 - A family history of early onset breast cancer or male breast cancer
 - Ashkenazi Jewish heritage

Genomics and a New Era of Treatment

- Tremendous need to understand and develop new ways to treat and manage cancer
- Every cancer may have a myriad of different genetic alterations
- Some patients may be more likely to develop recurrent disease or to respond to different treatments
- May also lead to a new means of customizing treatment to target certain defects within individual tumor cells