


Bioinformatics

Case Study

BRCA1

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Outline

- ❖ Breast Cancer Genes Located
- ❖ Cancer
- ❖ Breast and Ovarian Cancer
- ❖ Sporadic versus Familial Cancer
- ❖ Knudson Two-Hit
- ❖ BRCA1 and BRCA2 Locations
- ❖ BRCA Mutations

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Breast Cancer Genes Found



- BRCA1 (for BREast CAncer gene 1) was described in 1990 on chromosome 17, isolated in 1994
- BRCA2 was isolated on chromosome 13 in late 1994
- BRCA3?

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Cancer

All cancer involves changes in genes....

Threshold effect:

- During mitosis & DNA replication
 - mutations occur in the cell's genetic code
- Mutations are normally corrected by DNA repair mechanisms
- If repair mechanism or cell cycle regulation damaged
 - Cell accumulates too many mutations
 - reaches 'threshold'
 - tumor development


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Sporadic Cancer

- All cancer arises from changes in genes....
 - But NOT all cancer is inherited
- Most breast cancer is **sporadic** ~ 80%
 - Due to mutations acquired over a person's lifetime:
 - Cause unknown – multifactorial
 - Interaction of: age, environment, lifestyle (obesity, alcohol), chance, unknown factors
 - Sporadic cancer generally has a later onset

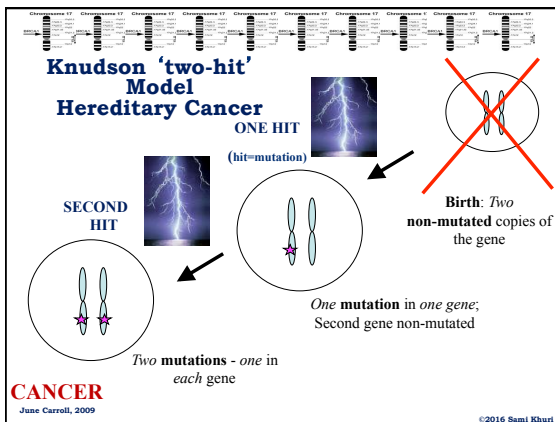
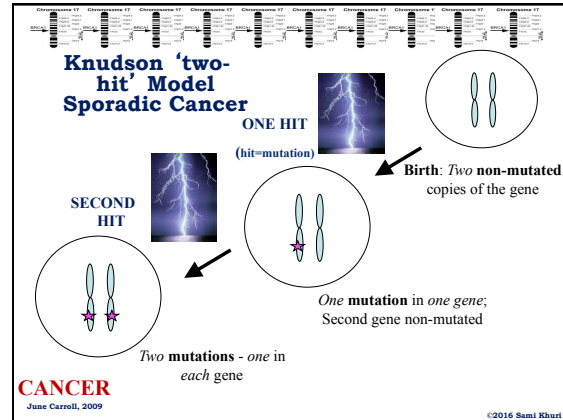
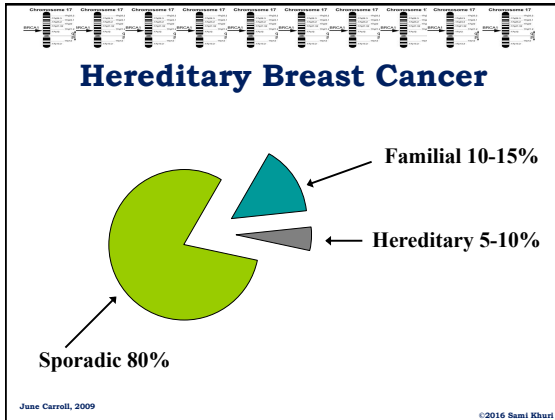
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Cancer Clustering in Families

- 11% lifetime risk of developing breast cancer
- ~20% of women with breast cancer have a family history:
- 10 -15% of breast cancer is **familial**:
 - Due to some factor in the family
 - Environmental
 - Undiscovered gene mutation
 - Chance
 - Generally not eligible for genetic testing
- 5-10% of breast cancer is **hereditary**:
 - Caused by an inherited gene mutation which causes increased risk for cancer
 - Variety of cancer syndromes
 - About 2/3 of these - BRCA 1 or BRCA 2 mutations
 - May be eligible for genetic testing

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People with Hereditary Cancer

- Have a higher risk of developing cancer
- Have a younger age of onset of cancer
 - Generally < 50 years of age
- Have multiple primary cancers

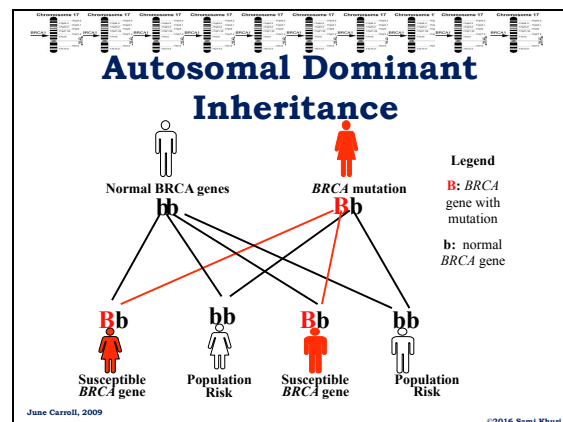
Hereditary cancer is less common in the general population than sporadic cancer

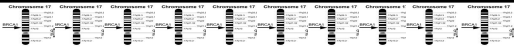
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Genes involved in Hereditary Breast/Ovarian Cancer

- > 2,600 mutations in:
 - *BRCA1* - chromosome 17
 - *BRCA2* - chromosome 13
- Autosomal dominant transmission
- Carrier frequency of *BRCA1* & 2 mutations
 - ~1/500 – 1/1,000 in general (Caucasian) population
 - 1/40 - 1/50 in Ashkenazi Jewish people
 - 3 common mutations in Ashkenazi Jews
 - Unique French Canadian mutations

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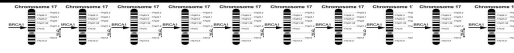


BRCA1 and BRCA2

What happens when their function is compromised ?

- Both genes are tumor suppressors:
 - Regulation of cell growth
 - Maintenance of cell cycle
- Mutation leads to:
 - Inability to regulate cell death
 - Uncontrolled growth, cancer

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BRCA Mutations

Estimated cancer risk by age 70

	BRCA Mutation Carriers	In General Population
Breast Cancer ♀ <i>BRCA1 & BRCA2</i>	50-85%	11%
Ovarian Cancer <i>BRCA1</i>	40-60%	1-2%
Ovarian Cancer <i>BRCA2</i>	10-20%	1-2%
Breast Cancer ♂ <i>BRCA2</i>	≤6%	Rare

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