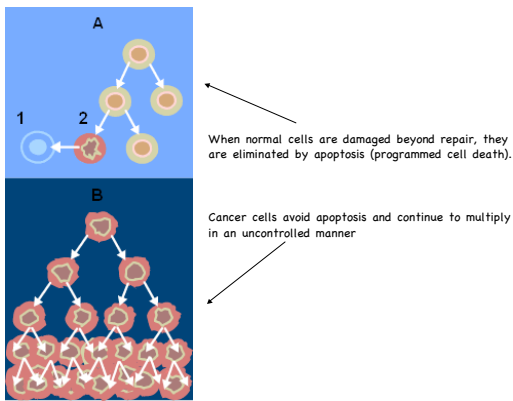
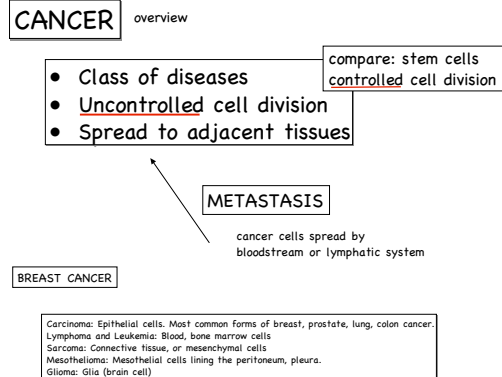


# SOMATIC MUTATIONS, GERM-LINE MUTATIONS, AND BREAST CANCER

READING: pp. 202-220



### NEW CASES OF CANCER

U.S. 2002

Site	Number of new cases
Skin	800,000
Breast (female)	203,500
Prostate	189,000
Lung	169,400
Colon-rectum	148,300
Urinary system	90,000
Uterus	52,300
Pancreas	30,300
Ovary	23,300

1/3 individuals will get some form of cancer  
older adults - 1/4 of all deaths due to cancer

## BREAST CANCER

(some demographics)

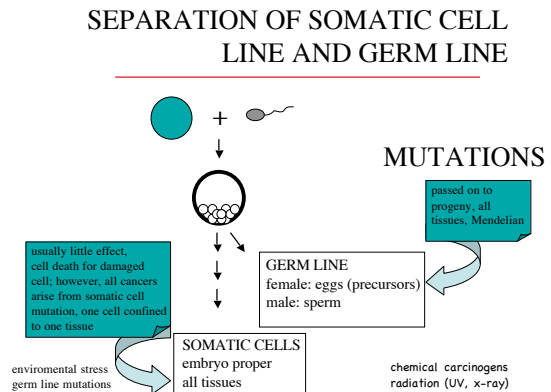
1 in 8 women expected to be diagnosed sometime during their lives

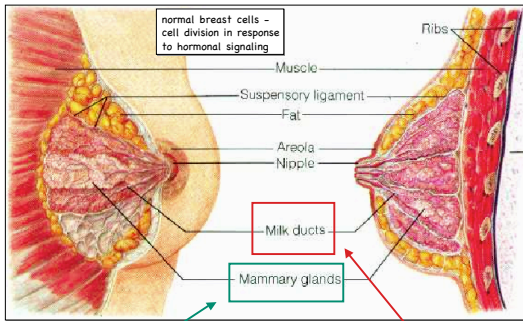
41,000 US women will die this year

Breast cancer occurs more often in white women than African American or Asian women

### AGE CONSIDERATIONS

- 12 y - Early menstruation - risk factor (estrogen)
- 30 y - Late childbearing (1st child) - risk factor (estrogen)
- 35 y - Breast cancer uncommon below this age
- 40 y - Regular mammograms (yearly)
- 40 y - Many breast cancers estrogen-dependent (35%)
- 50 y - Most cancers occur over this age
- 55 y - Late menopause - risk factor (estrogen)
- 60 y - Risk for breast cancer especially high (NIH website)

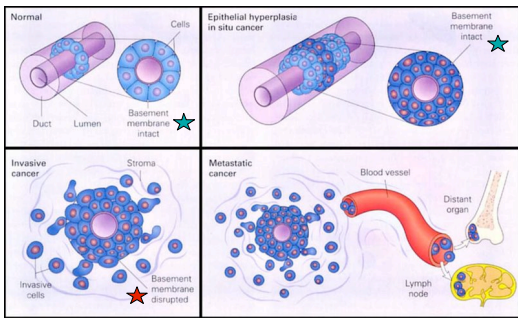
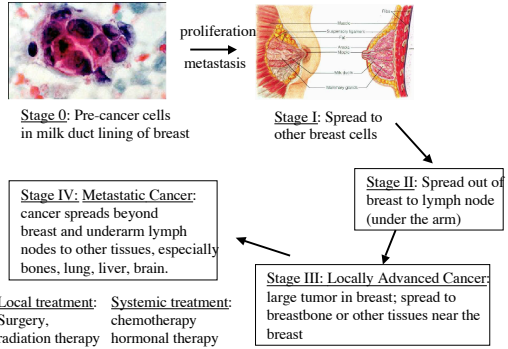




**LOBULAR CARCINOMA**  
begins in the lobules of the mammary glands

**DUCTAL CARCINOMA**  
most common type of breast cancer - begins in the lining of the ducts

### BREAST CANCER PROGRESSION



Time line of breast cancer suggesting probable heterogeneity. Primary breast cancers begin as single (or more) cells which have lost normal regulation of differentiation and proliferation but remain confined within the basement membrane of the duct or lobule. As these cells go through several doublings, at some point they invade through the basement membrane of the ductule or lobule and ultimately metastasize to distant organs.

### TUMORS

abnormal growth of tissue

**BENIGN TUMORS**      **CANCEROUS TUMORS**

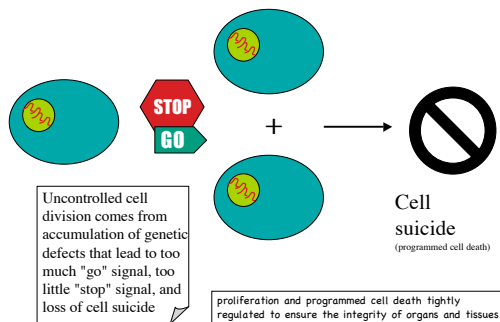


Self-contained. Do not spread to other tissues. Not invasive. Cause problems by increasing in size until they interfere with the function of neighboring organs.

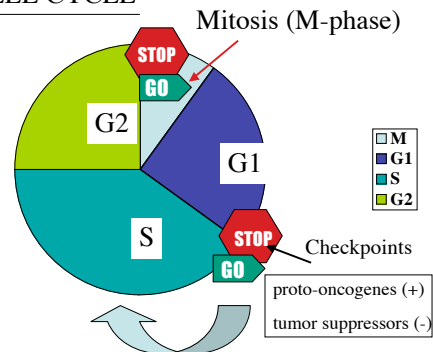
Cells divide with increasingly more aggressive growth until completely out of control. Acquire ability to spread beyond prescribed boundaries. Cells can detach from primary tumor and move to other sites in the body. Can invade tissues to form new malignant tumors.

Single cell + clonal descendants.  
Accumulation of multiple mutations in array of genes (4-7 somatic mutations minimum)

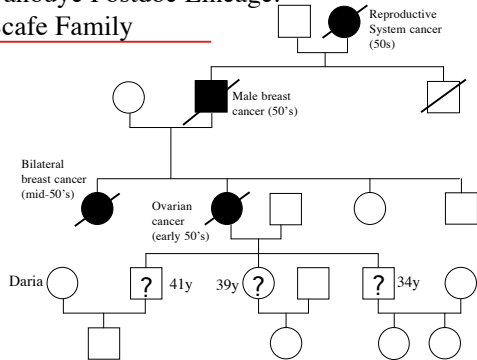
### CELL PROLIFERATION



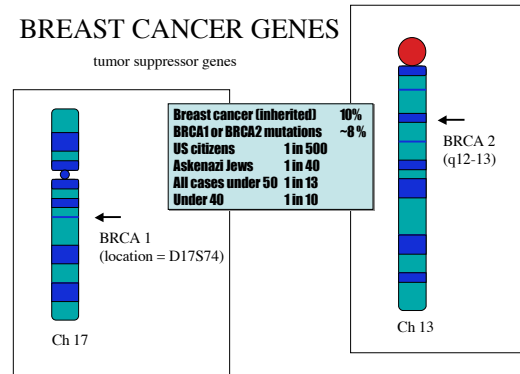
### THE CELL CYCLE



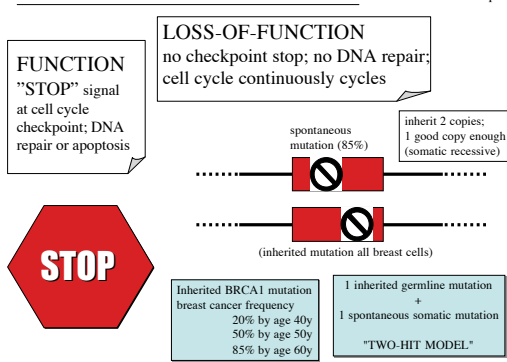
Tanouye Postdoc Lineage:  
Scafe Family



BREAST CANCER GENES

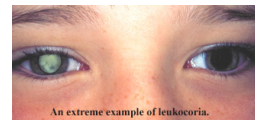


TUMOR SUPPRESSOR GENES



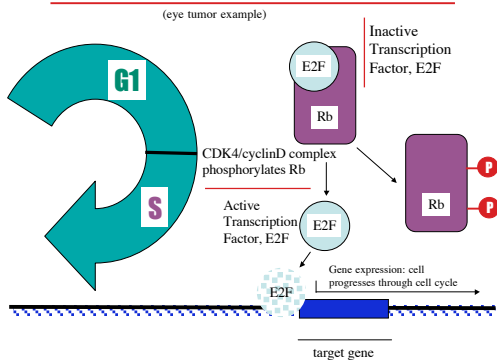
*pRb was the first 'classic' tumor suppressor*

The disease; retinoblastoma



Retinoblastoma is a cancer which develops in the cells of the retina  
-one of the less common cancers of childhood  
-accounts for only about 3 out of every 100 cancers occurring in children under the age of 15 years  
Children present with:  
-an abnormal appearance of the pupil which reflects light as a white reflex, like a cat's eye.  
-a squint.

TUMOR-SUPPRESSOR GENE: Rb (Retinoblastoma)



G<sub>1</sub>-to-S TRANSITION

CDK2  
CDK4  
cyclinA  
cyclinD  
cyclinE

Some proteins responsible for progression through transition and checkpoint.

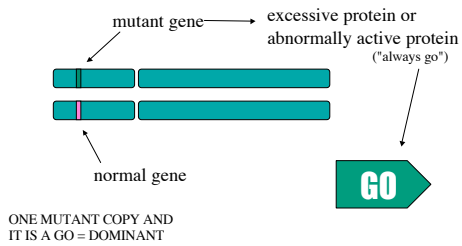
ALL ARE CANCER GENES

Rb (retinoblastoma; E2F inhibitor)  
E2F (transcription factor)  
p21  
p53

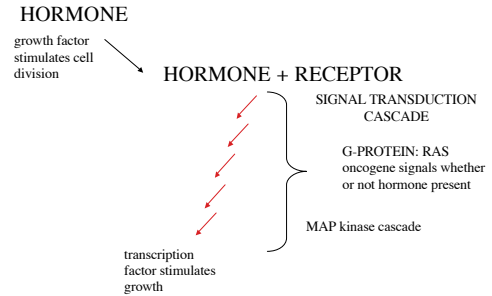
CDK enzymes are cyclin-dependent protein kinases; control the activity of other proteins by phosphorylating them

Cyclins are proteins necessary for CDK activity

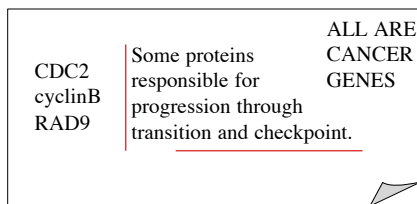
## DOMINANT ONCOGENE ("GAIN-OF-FUNCTION" MUTATION)



## ONCOGENE: RAS



## G<sub>2</sub>-to-M TRANSITION



## CANCER GENES

Accumulation of multiple mutations  
Potential cancer genes - about 100 genes

- 1) Inappropriate signals about need for cell division (hormonal signaling pathways: growth factors)
- 2) Malfunctions in CDK-cyclin complexes controlling cell cycle transitions
- 3) Checkpoint breakdowns leading to DNA instability
- 4) Loss of programmed cell death (cell suicide)