

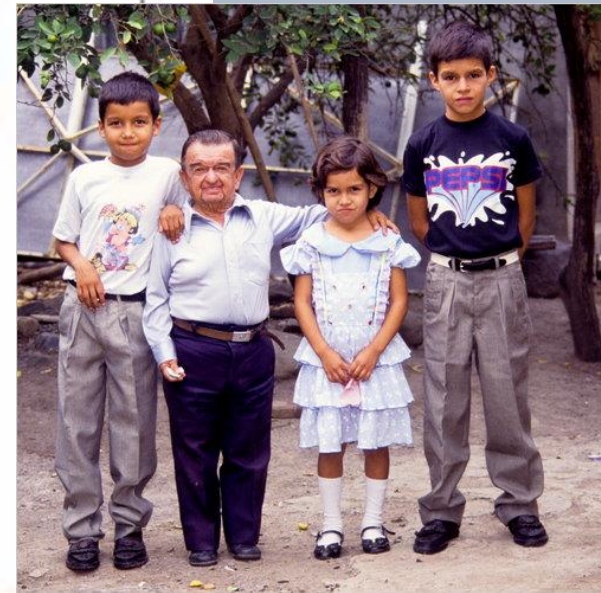
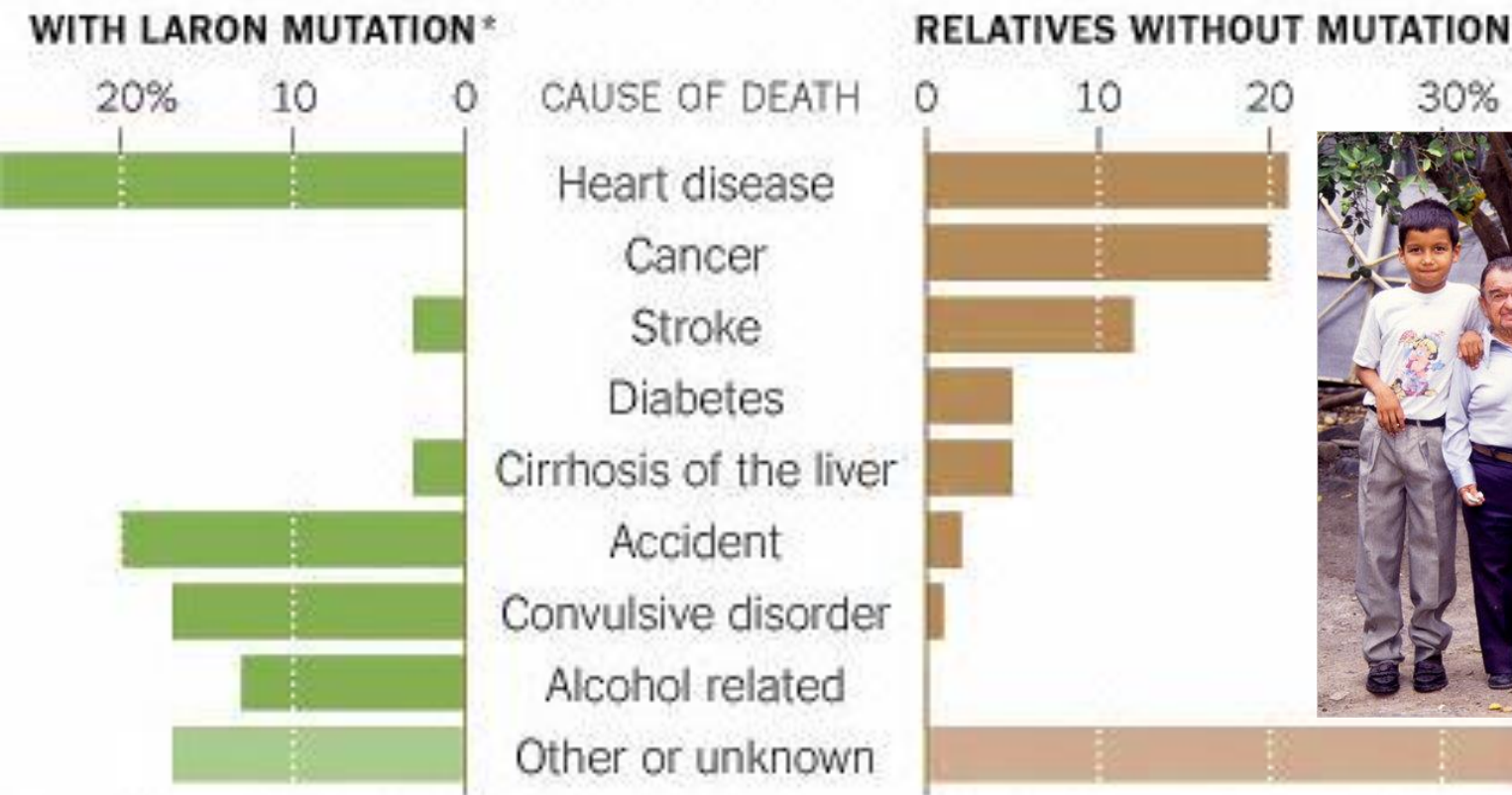


Lecture 10: Heredity and Cancer

Genetic Mutation Limits Cancer in Ecuador

A Rare Mutation

Researchers in Ecuador tracked a group of villagers with Laron syndrome, a genetic mutation that limits the effects of growth hormone and causes a type of dwarfism. Villagers with the mutation are more likely to die from accidents or alcohol than their relatives without the mutation, but after 24 years none of them had died from cancer or developed diabetes.



*Because of high childhood mortality, deaths among children under 10 are excluded.

Source: Science Translational Medicine

THE NEW YORK TIMES

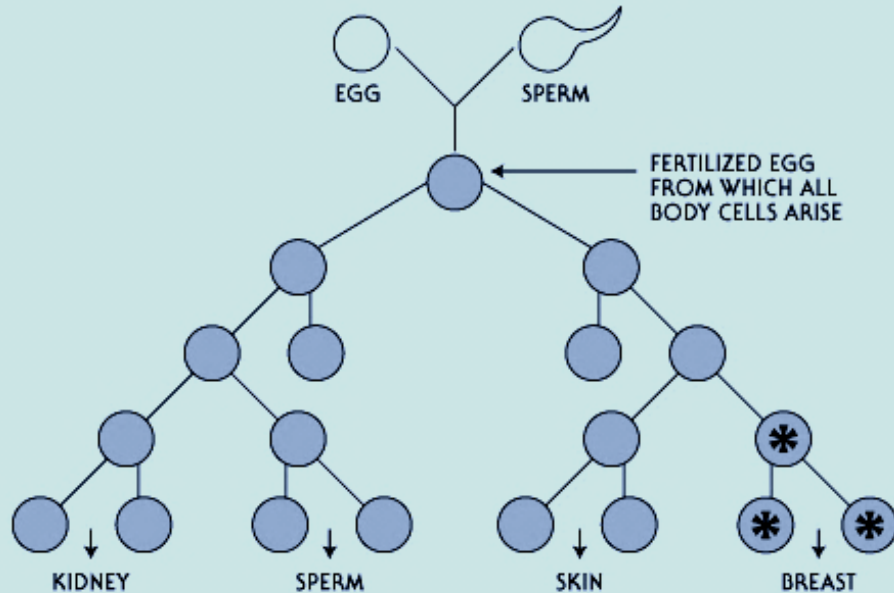
Heredity and Cancer Risks

A family history that ***might*** indicate an inherited gene mutation would include two or more of the following points:

- ☐ cancer in several closely related people, on the same side of the family, in several generations
- ☐ cancer at younger ages than usual (e.g., breast cancer in your 30s)
- ☐ more than one diagnosis of cancer in the same person
- ☐ specific types of cancer that are linked to specific genes (e.g., breast cancer & ovary cancer, or colon cancer & endometrial cancer)

Germ Line VS Somatic Cancer

NEW CHANGE TO THE GENES IN THE CELLS OF THE BODY (SOMATIC MUTATIONS)

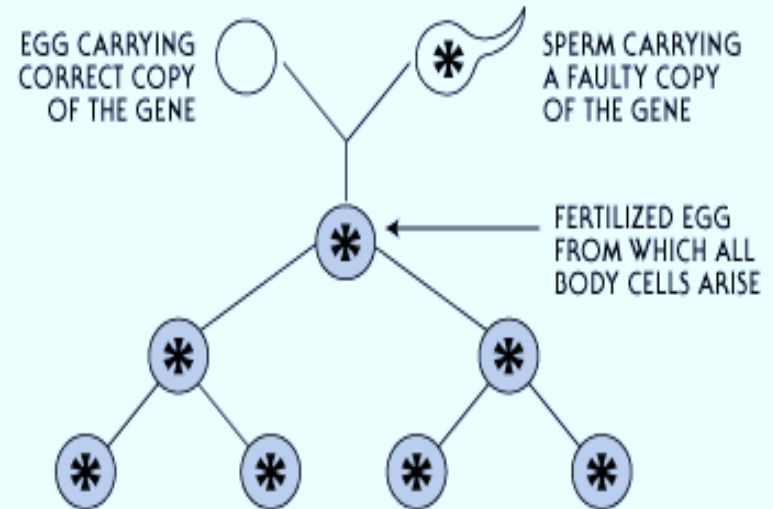


KEY

⬤ BODY CELLS CONTAINING FAULTY (MUTATED) GENE

● BODY CELL CONTAINING CORRECT COPY OF GENE

INHERITANCE OF A MUTATION IN A GERM CELL (EGG OR SPERM)



KEY

⬤ BODY CELLS CONTAINING FAULTY (MUTATED) GENE

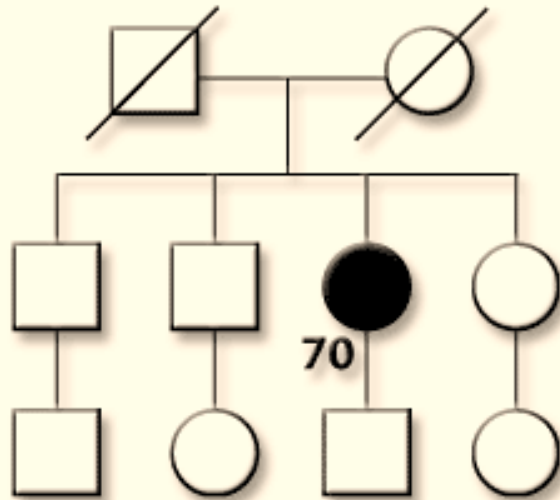
* FAULTY (MUTATED) GENE IN ALL CELLS

Mutations in somatic cells cannot be inherited

Inheritance of a mutation in a germ cell (egg or sperm)

Hereditary Cancer

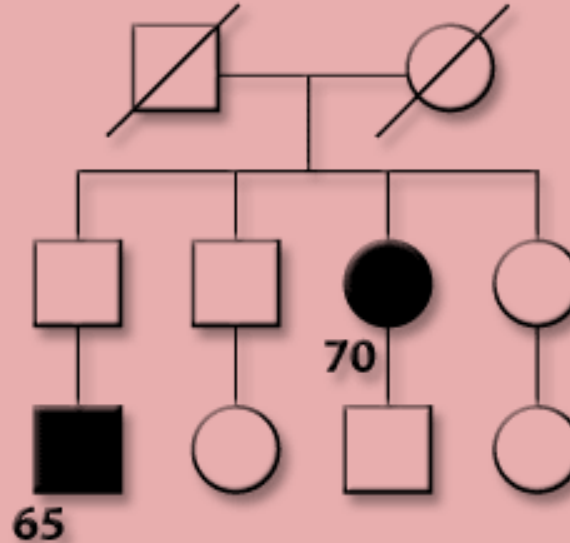
Sporadic Cancer History



Key: □ = Male
○ = Female
■ ● = Persons with Cancer
◻ ◯ = Deceased

Numbers are ages of onset of cancer.

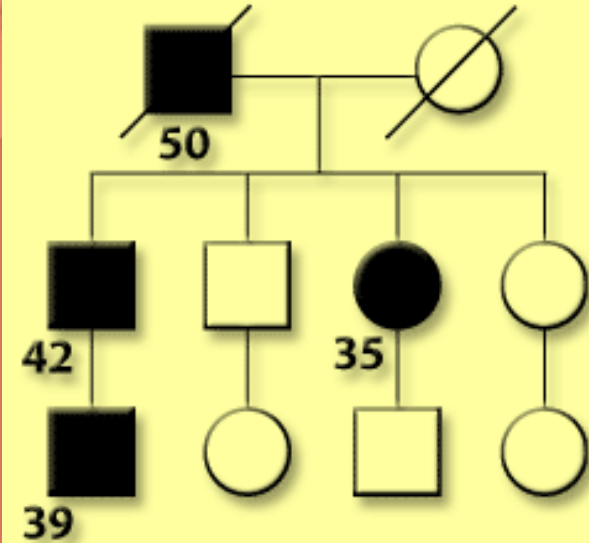
Familial Cancer History



Key: □ = Male
○ = Female
■ ● = Persons with Cancer
◻ ◯ = Deceased

Numbers are ages of onset of cancer.

Hereditary Cancer History



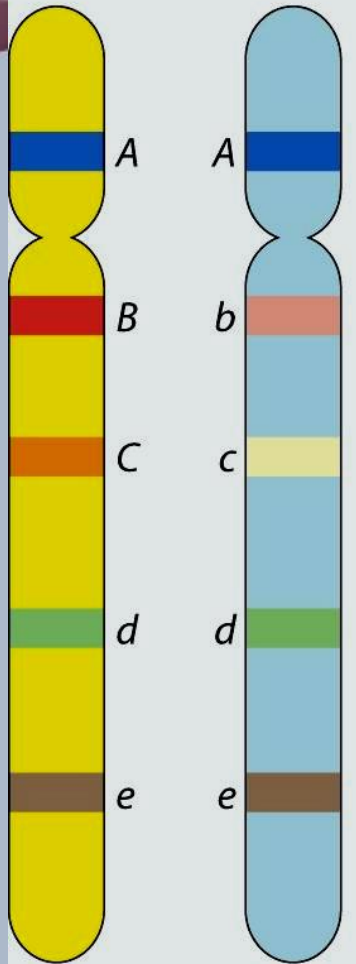
Key: □ = Male
○ = Female
■ ● = Persons with Cancer
◻ ◯ = Deceased

Numbers are ages of onset of cancer.

- ❑ Cancer resulting from inheritance generally presents as an autosomal dominant trait of a germline alteration in one gene, conferring a genetic susceptibility to the development of cancer.

Genetic Terminology

Homologous pair of chromosomes



<u>Genes present</u>	<u>Trait expressed</u>	<u>Penetrance</u>
Homozygous dominant (AA)	Dominant trait A	Complete
Heterozygous (Bb)	Dominant trait B	Complete
Heterozygous (Cc)	Dominant trait C (in 90% of individuals)	Incomplete (90%)
Homozygous recessive (dd)	Recessive trait d	Complete
Homozygous recessive (ee)	Recessive trait e (in 80% of individuals)	Incomplete (80%)

Alleles – different versions of a gene

Penetrance – Frequency with which an allele yields an expected trait in a population

Autosomal Dominant Disorder

Father with abnormal gene on autosomal chromosome



Mother with normal autosomal chromosome



Parents:

AA

AA

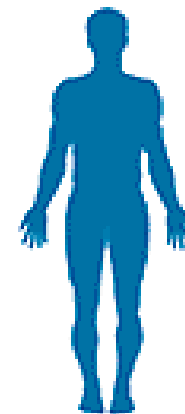
Offspring:

AA

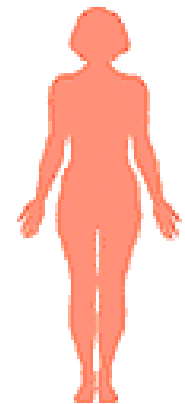
AA

Aa

Aa



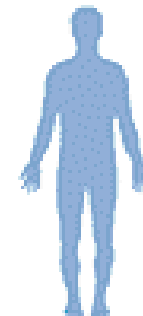
Affected Father



Normal Mother



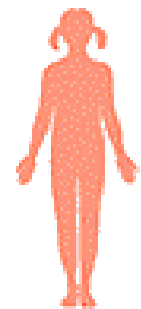
Affected Female Child



Normal Male Child



Affected Male Child

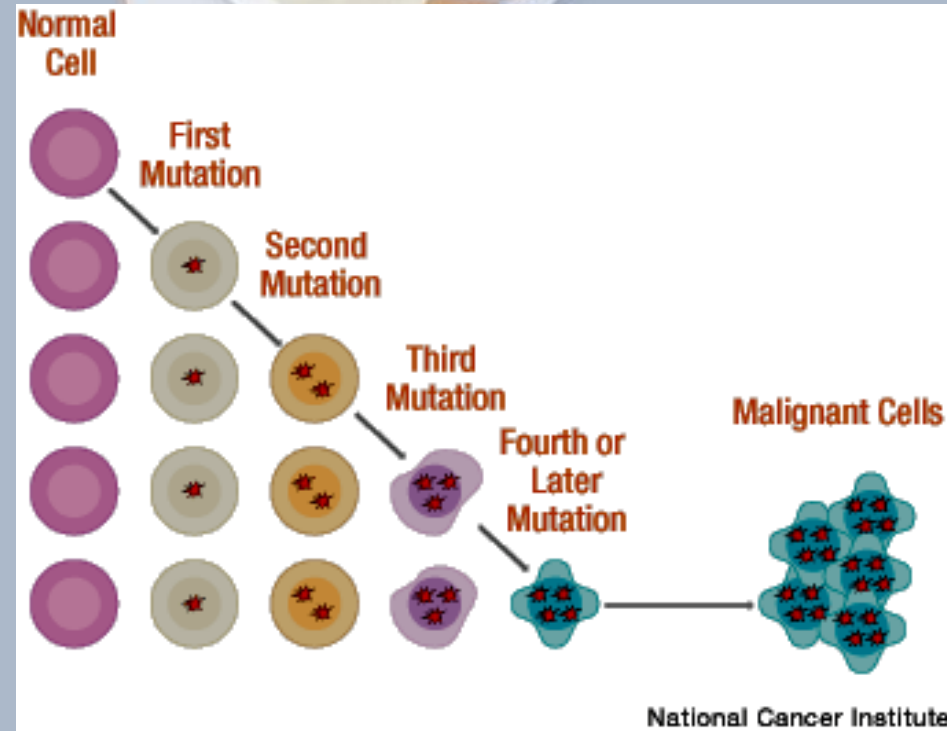


Normal Female Child

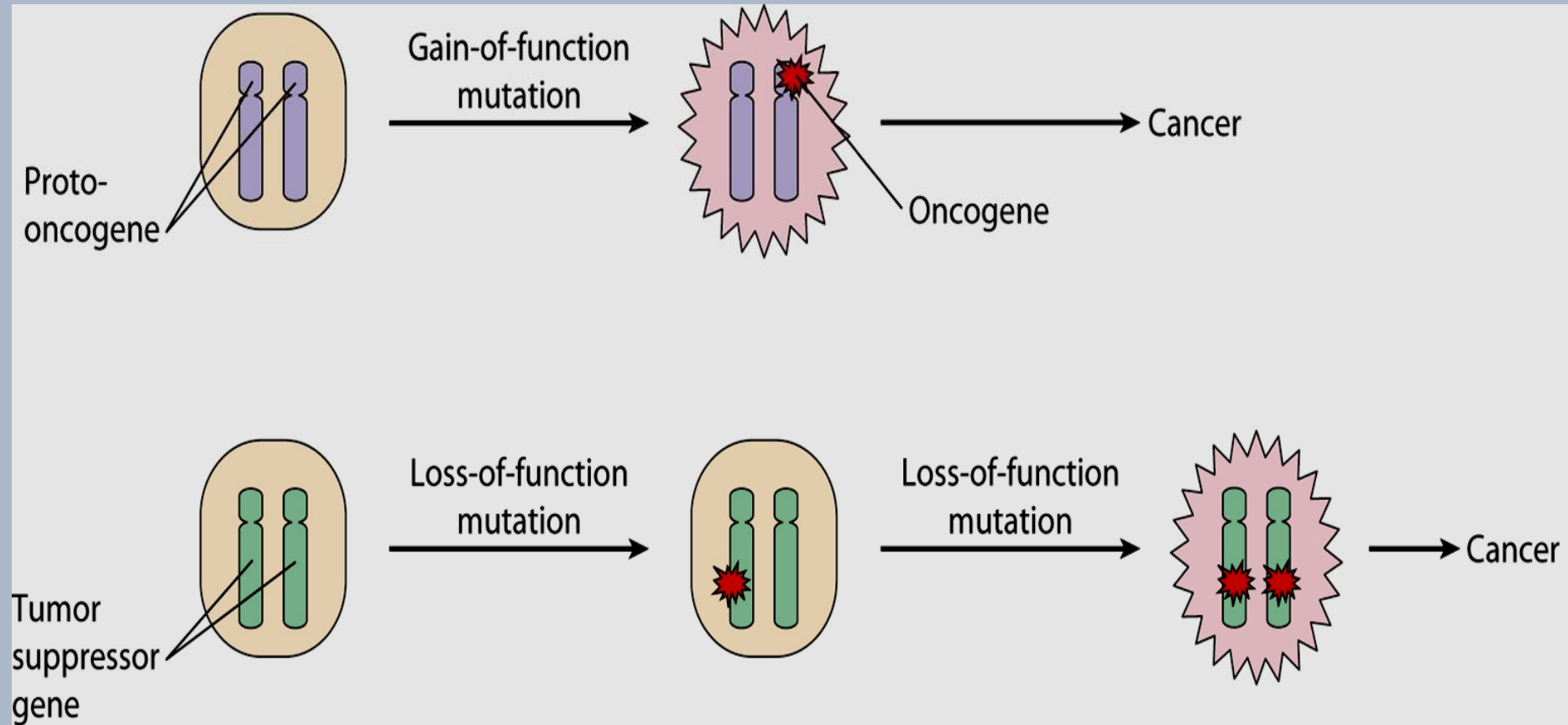
Each pregnancy bears a 50-50 chance of carrying the abnormal gene

The Facts about Inherited Cancer

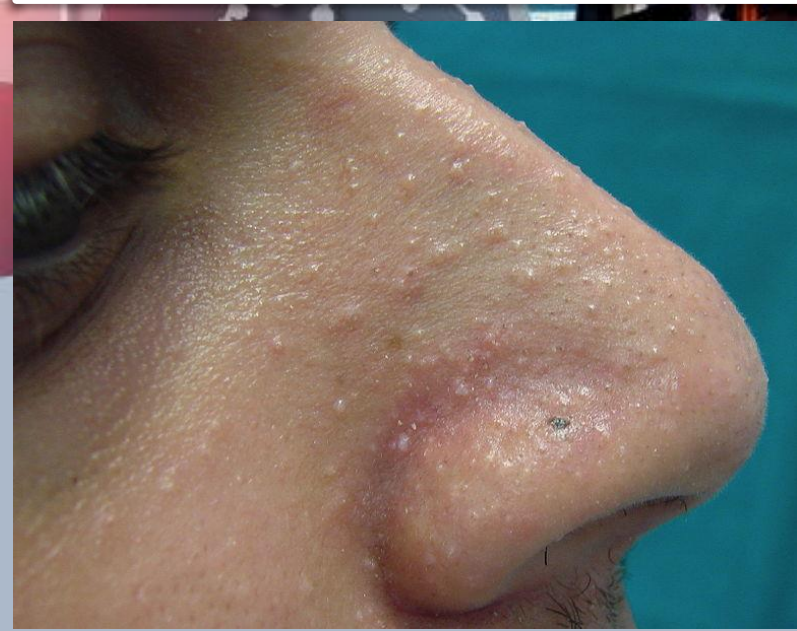
- ❑ Only 5-10% of all cancers are related to an inherited gene mutation
- ❑ Inheriting the gene mutation does NOT mean that the child is born with cancer
- ❑ The child inherits a higher risk of developing cancer sometime during his/her life
- ❑ Many genes are involved in cancer formation, therefore, not everyone who inherits a gene mutation will develop cancer



Behavior of Proto-oncogenes Compared with Tumor Suppressor Genes in Cancer



Cowden Disease (Multiple Hamartoma Syndrome)



Characteristics:

- multiple hamartomatous lesions (benign, or noncancerous, tumors of the skin and other organs)

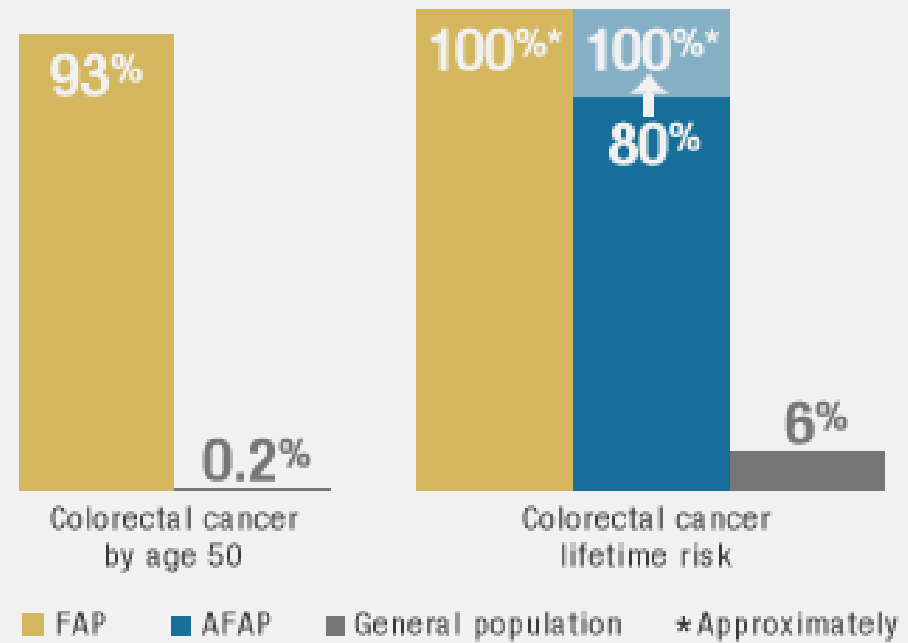
- Inherited mutations in the PTEN gene have been found in ~80% of people with Cowden syndrome
- Usually present by the late 20s
- Increased risk of breast (average age of onset ranging from 38 to 46 years), thyroid, endometrial and uterine cancer)

Inherited Polyposis Syndromes

- ❑ The majority of colorectal cancers are sporadic, or not caused by inherited risk factors.
- ❑ ~10% of cases are inherited, (caused by single genes that are passed on in families).
- ❑ Adenomatous polyposis syndromes are inherited colorectal cancer syndromes that are associated with multiple precancerous (*adenomatous*) polyps in the colon

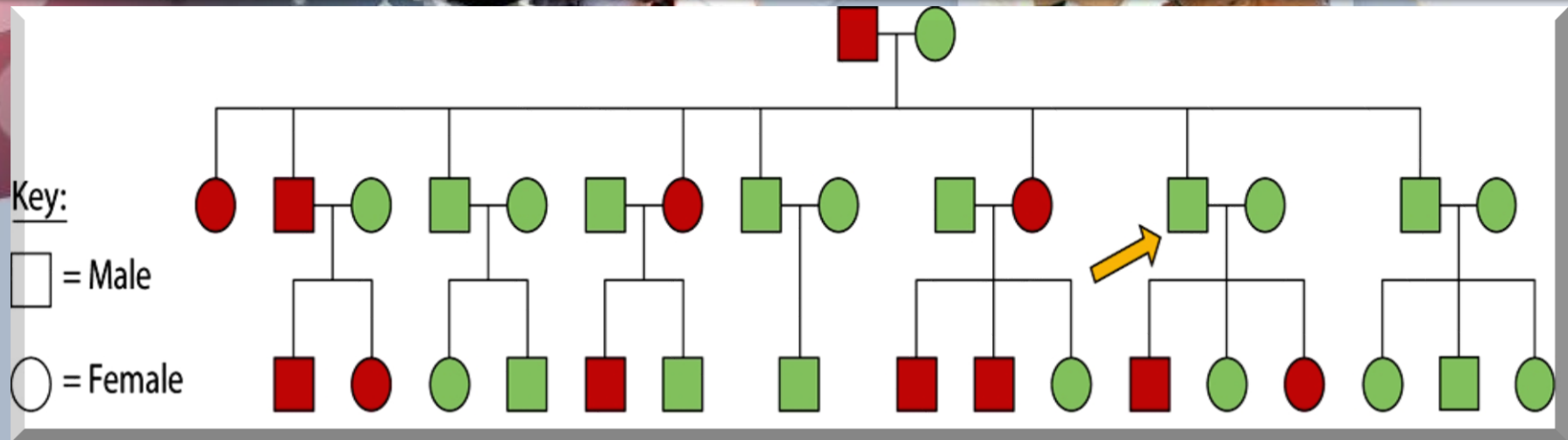


APC Mutation Increases the Risk of Cancer



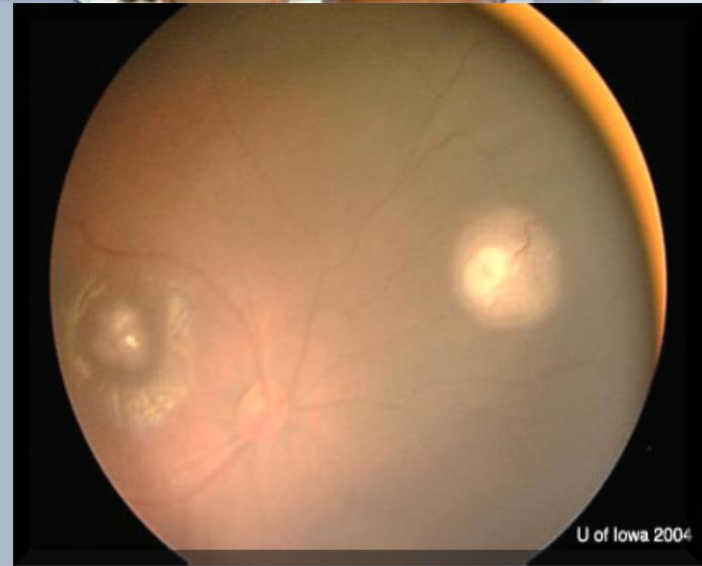
Familial Adenomatous Polyposis (FAP). Attenuated FAP (AFAP).

Pedigree Typical of Familial Retinoblastoma

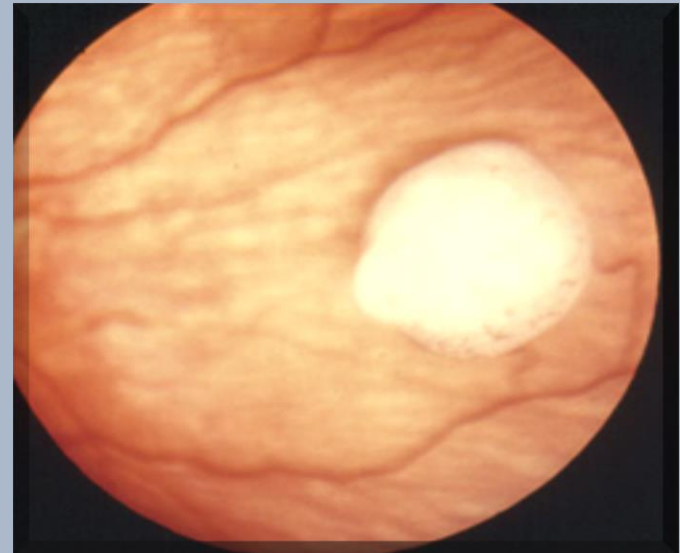


- ❑ A normal child has a 1-in-20,000 chance of developing retinoblastoma
- ❑ In families of retinoblastoma survivors, ~**50%** of the children develop the disease
- ❑ ~**40%** of retinoblastoma cases are familial, the rest are sporadic
- ❑ Children with **familial** form develop **multiple tumors**; **sporadic** cases typically have a **single tumor**

Retinoblastoma

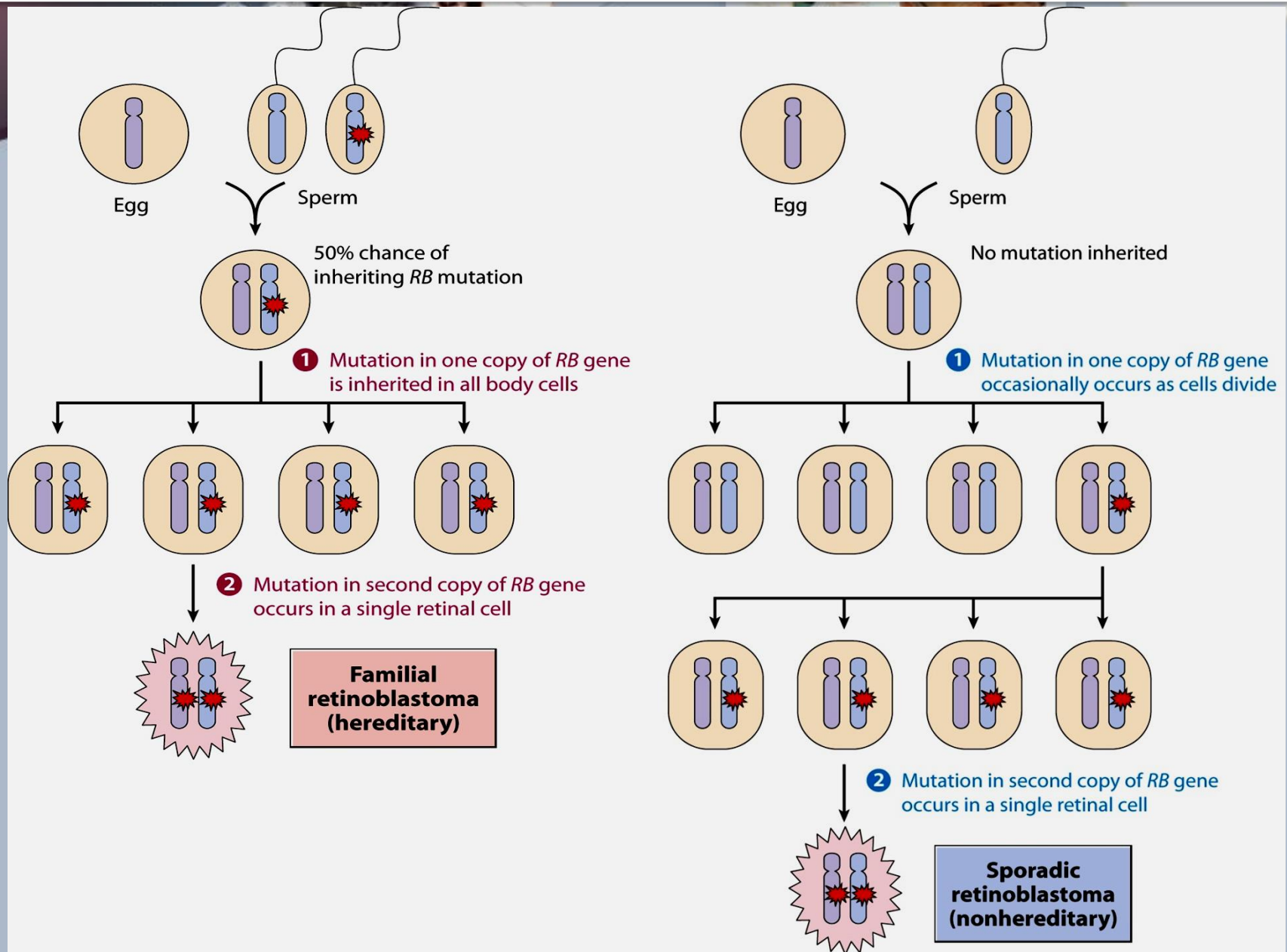


Familial Retinoblastoma Multiple tumors

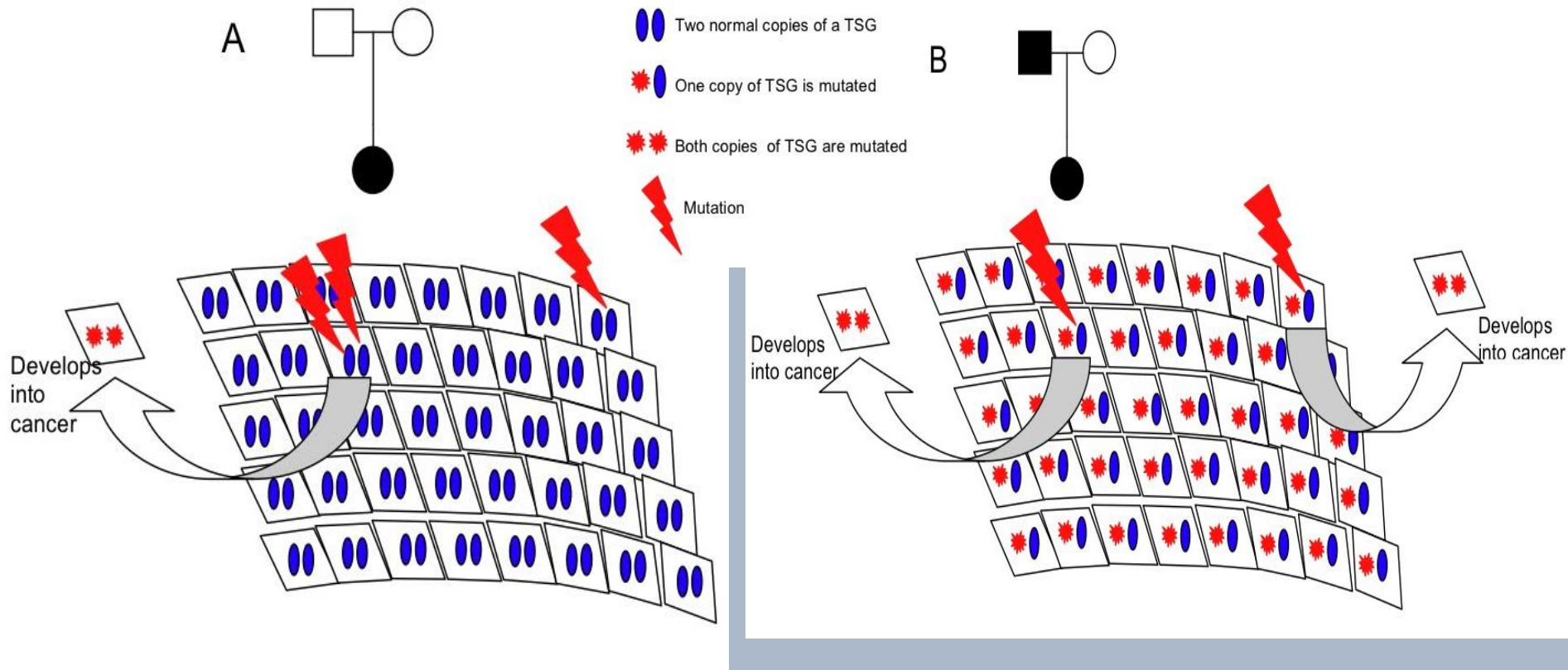


Possible sporadic Retinoblastoma with single large tumor

Hereditary and Non-hereditary forms of Retinoblastoma

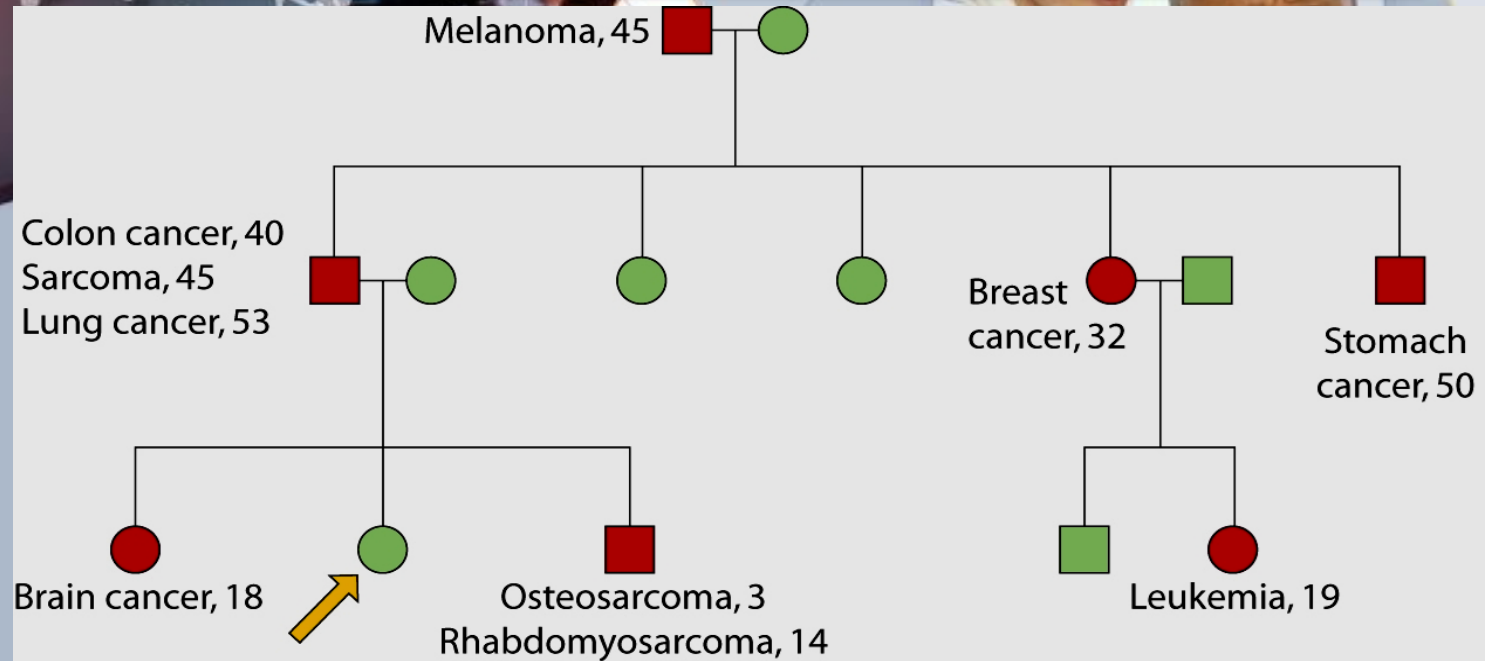


Retinoblastoma and the Two-Hit Model for Cancer



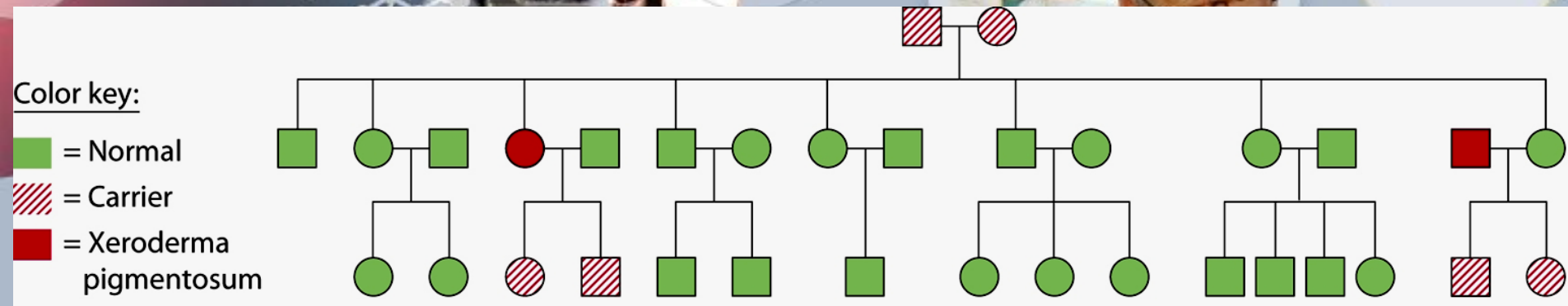
A) An individual with sporadic retinoblastoma. A retinoblastoma develops in a cell that has undergone two somatic mutations in the same cell. Another retinoblast that had a similar mutation only has one mutated copy of the *RB* gene and does not develop into a cancer. B) An individual with hereditary retinoblastoma. Two primary retinoblastomas develop independently in two cells that receive a second hit that mutated the normal copy of the *RB* gene in cells that already had one mutated copy of the gene.

Li-Fraumeni Syndrome



- ☐ Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex, lung and brain.
- ☐ Extremely rare condition, only a few hundred families worldwide
- ☐ Susceptibility to cancer in general and is transmitted from parent to offspring
- ☐ These individuals have a mutation in one copy the **p53** gene

Typical Xeroderma Pigmentosum Pedigree



- ❑ Xeroderma Pigmentosum requires 2 copies of mutant gene to be inherited, one from each parent
- ❑ Carriers exhibit no disease symptoms, but can pass gene on to children
- ❑ Each child will have a 50% chance of inheriting mutant gene from each parent (overall probability is $50\% \times 50\% = 25\%$)

Xeroderma Pigmentosum



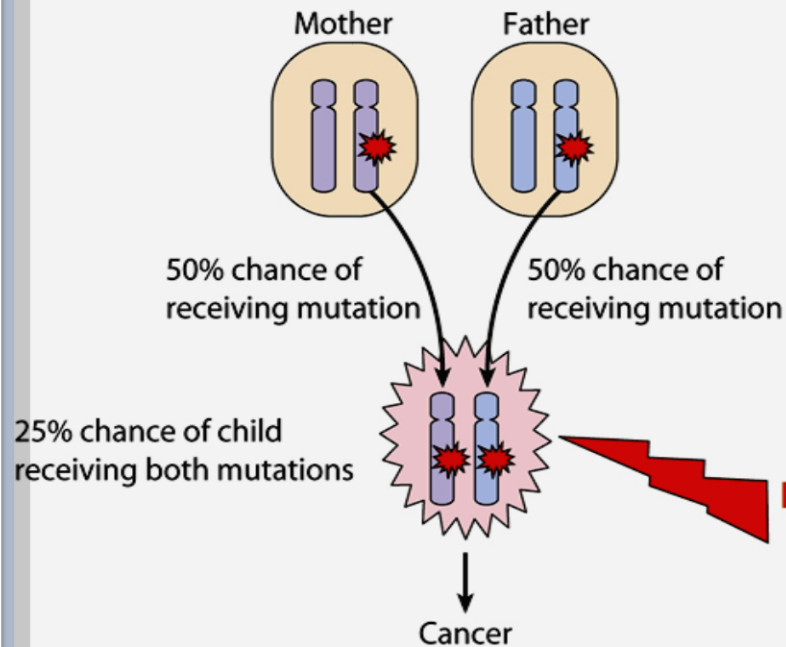
- ❑ Patients are sensitive to UV; sunlight could be fatal
- ❑ Suit designed by NASA
- ❑ **Sunlight exposure leads to skin cancer**
- ❑ Camp Sundown in upstate NY allow kids to participate in normal recreation
- ❑ 2 copies of the same gene inherited from each parent



Xeroderma Pigmentosum

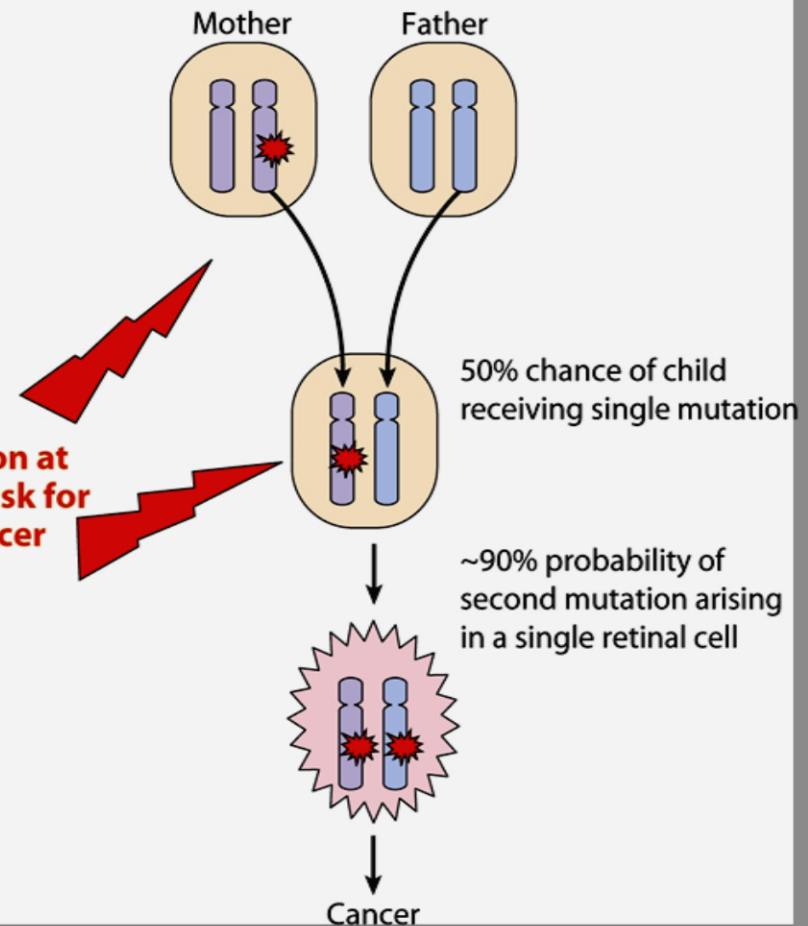
(a) Recessive cancer-risk syndrome.

In hereditary cancer-risk syndromes exhibiting a recessive pattern of inheritance, such as xeroderma pigmentosum, two defective copies of a tumor suppressor gene must be inherited to create a high risk of developing cancer.

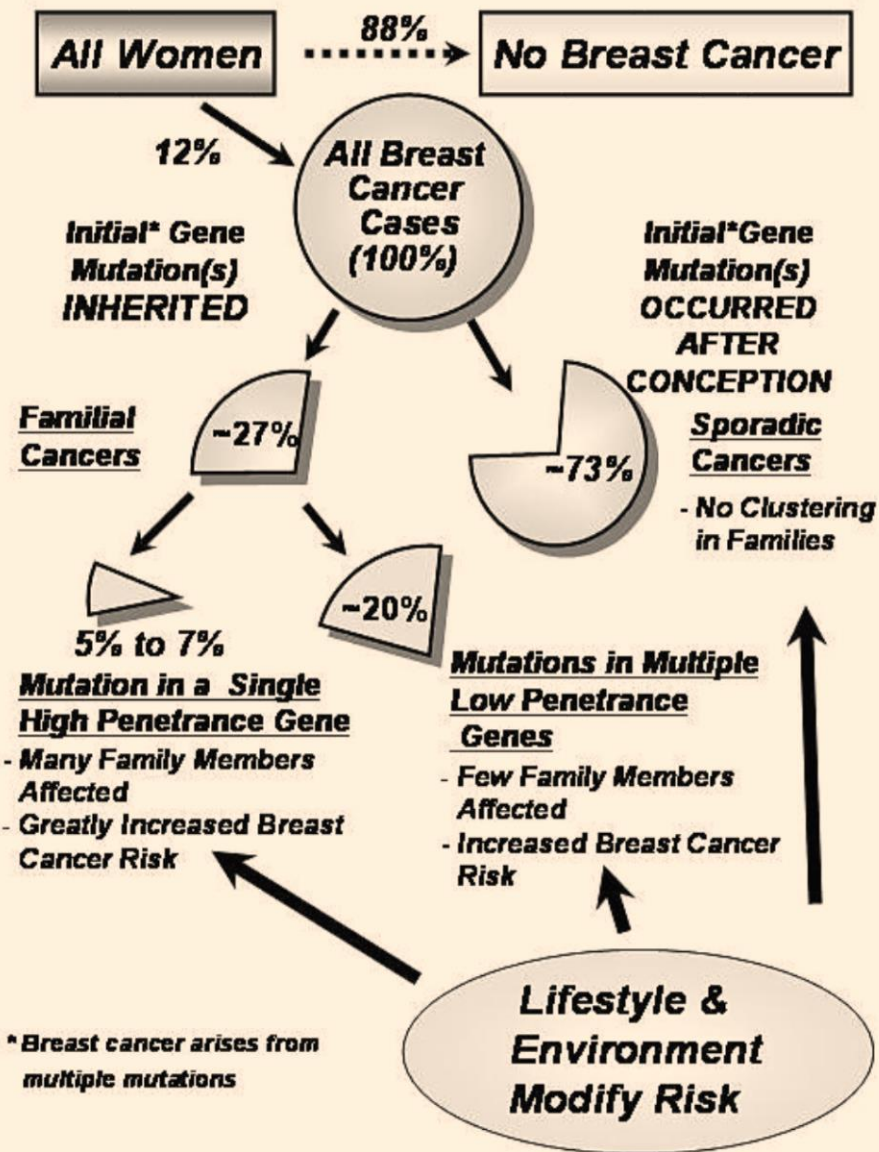


(b) Dominant cancer-risk syndrome.

In cancer-risk syndromes exhibiting a dominant pattern of inheritance, such as familial retinoblastoma, inheriting a single defective tumor suppressor gene is sufficient to confer a very high risk of developing cancer. However, mutation of the second copy of the gene is required before cancer actually arises.



Inheritance and Breast Cancer



- ❑ Risk between identical and non-identical twins has allowed a good estimate of how much of all breast cancer risk is inherited
- ❑ Data from twin and cancer registries in Sweden, Denmark, and Finland (547 pairs of identical twins and 1075 pairs of non-identical twins) reported that about 25-27% of the total risk of breast cancer was due to inherited factors
- ❑ Women with family history of breast cancer make up only 5 to 7 percent of all women with breast cancer

Hereditary versus Sporadic Breast Cancer

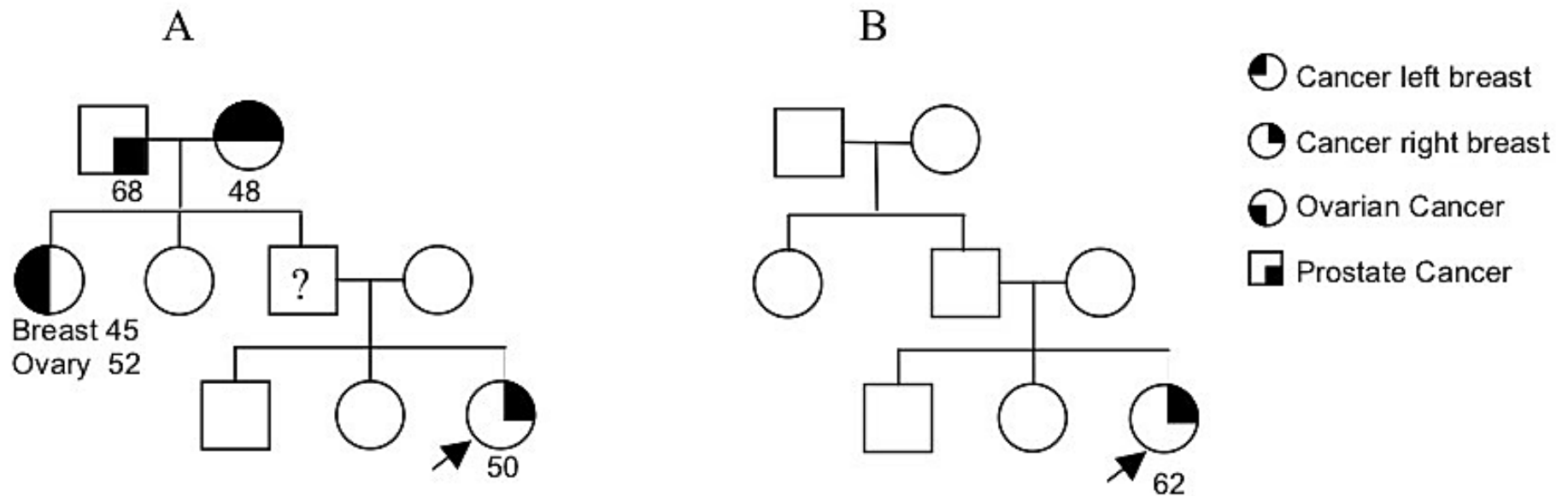


Figure 1. Families with (A) hereditary breast cancer due to a *BRCA1* mutation, and (B) sporadic breast cancer. Squares are men, circles females, horizontal lines connecting the midpoints of symbols designate couples, with their children connected below by vertical lines. Partially filled symbols are individuals with various cancers, with the age at which the cancer was diagnosed shown below each symbol. Arrow points to the individual who brought the family to our attention.

Inheritance and Breast Cancer

Of People Who Develop Breast Cancer



-  5% Have a Hereditary Syndrome
-  20% Have a Familial Risk
-  75% Have No Strong Family History



Role of xenoestrogens and endogenous sources of estrogens on the occurrence of premenopausal breast cancer in Iran.

Bidgoli SA, Eftekhari T, Sadeghipour R.

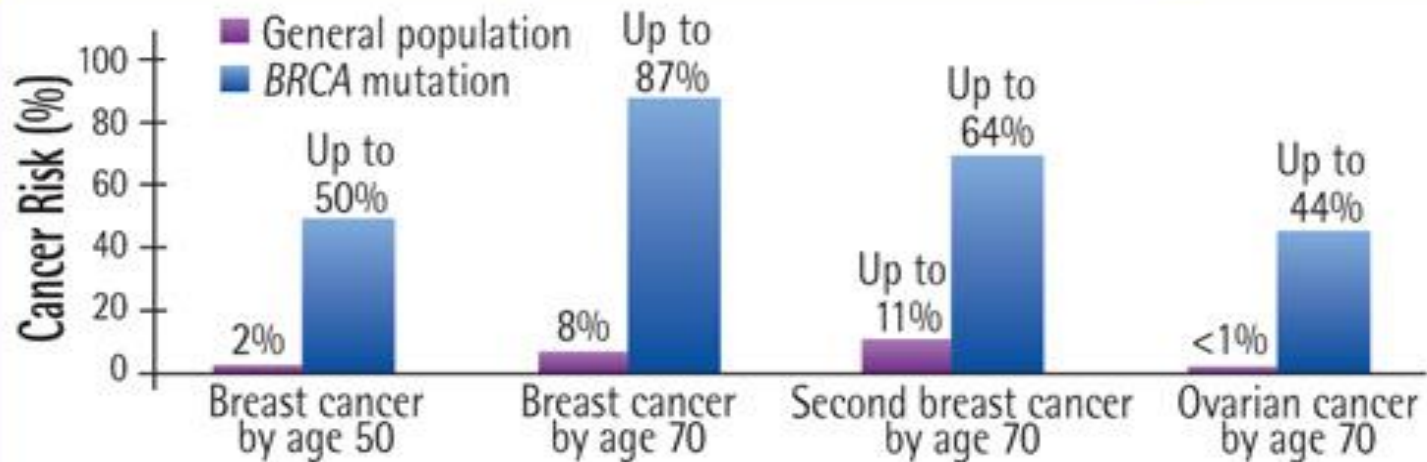
Toxicogenomics Lab, Faculty of Pharmacy, Islamic Azad University, Tehran, Iran E-mail arbabi.s@iaups.ac.ir.

Abstract

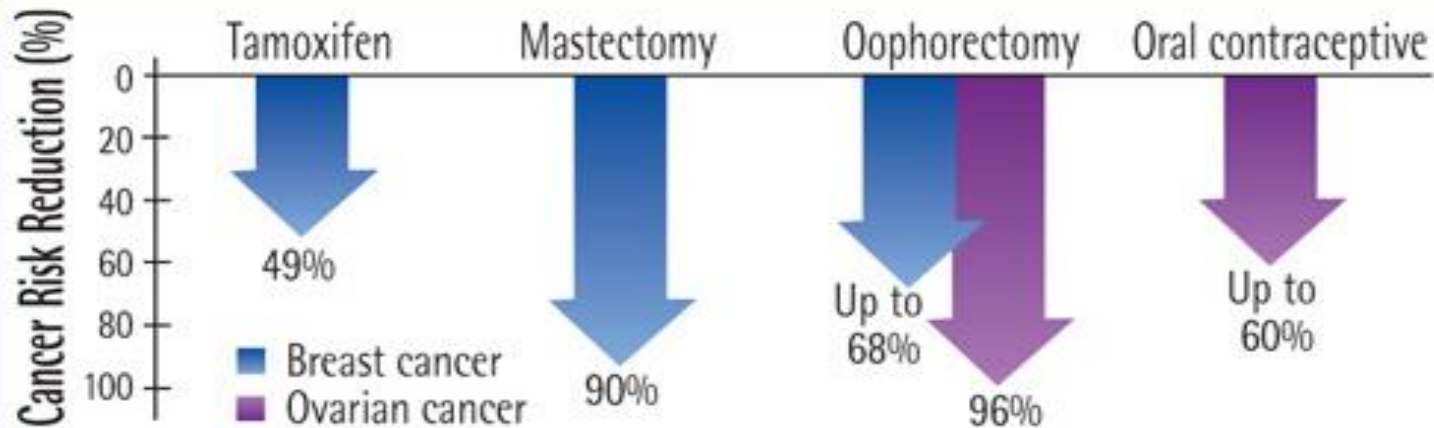
Breast cancer affects Iranian women one decade younger than their counterparts in other countries and the underlying risk factors have remained controversial. The aryl hydrocarbon receptor (AhR) mediates endocrine disruptive activities of polyaromatic hydrocarbons (PAHs) and dioxins, which may compromise ovarian functions of women in polluted environments. This study focused on tissue expression levels of AhR and associations with exposure to chemicals with estrogen-like activities (xenoestrogens) and other reproductive factors in premenopausal breast cancer patients. Fifty cases who underwent surgery from June 2009 to June 2010 were matched with 100 controls by age and hospital records. AhR overexpression was detected in 87% of epithelial cells of young breast cancer patients. Living near factories generating PAHs and dioxins was considered as a major risk factor in premenopausal breast cancer ($p=0.001$, $OR=4.8$). History of idiopathic infertility was identified as a second significant risk factor ($p=0.002$, $OR=3.50$), which could be affected by endogenous estrogen levels. Long term (>5 yrs) consumption of oral contraceptive pills was identified as the third most important risk factor ($p=0.006$, $OR=2.27$). Adiposity and abnormal weight gain after 18 years were considered as two major background factors, which may contribute to the levels of endogenous estrogens. Direct and indirect exposure to cigarette smoke ($p=0.005$, $OR=1.43$) was considered as a weak risk factor without association with AhR levels. It seems that AhR overexpression is affected by exposure to xenoestrogens and by adiposity. Early occurrence of breast cancer in Iran may be a result of interactions between hormonal and environmental factors.

Inheritance and Breast Cancer

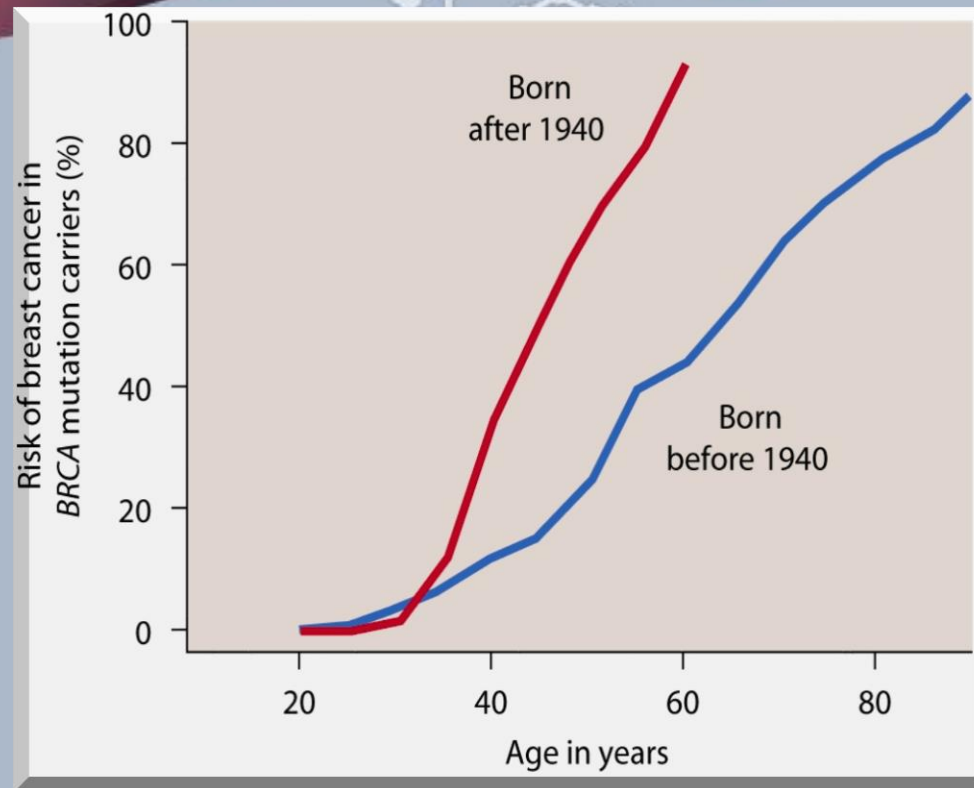
Mutations Dramatically Increase the Risk of Developing Cancer



Reduce Risk and Preempt Cancer with Proven Medical Management



Effect of Birth Year on Breast Cancer Risk from BRCA Mutations



- ❑ Women born **after 1940** carrying mutations in *BRCA 1* or *2* genes have higher breast cancer rates than women born **before 1940** who carry the same mutations
- ❑ This difference indicates that non-genetic factors influence breast cancer risks even in individuals who inherit high risk mutations

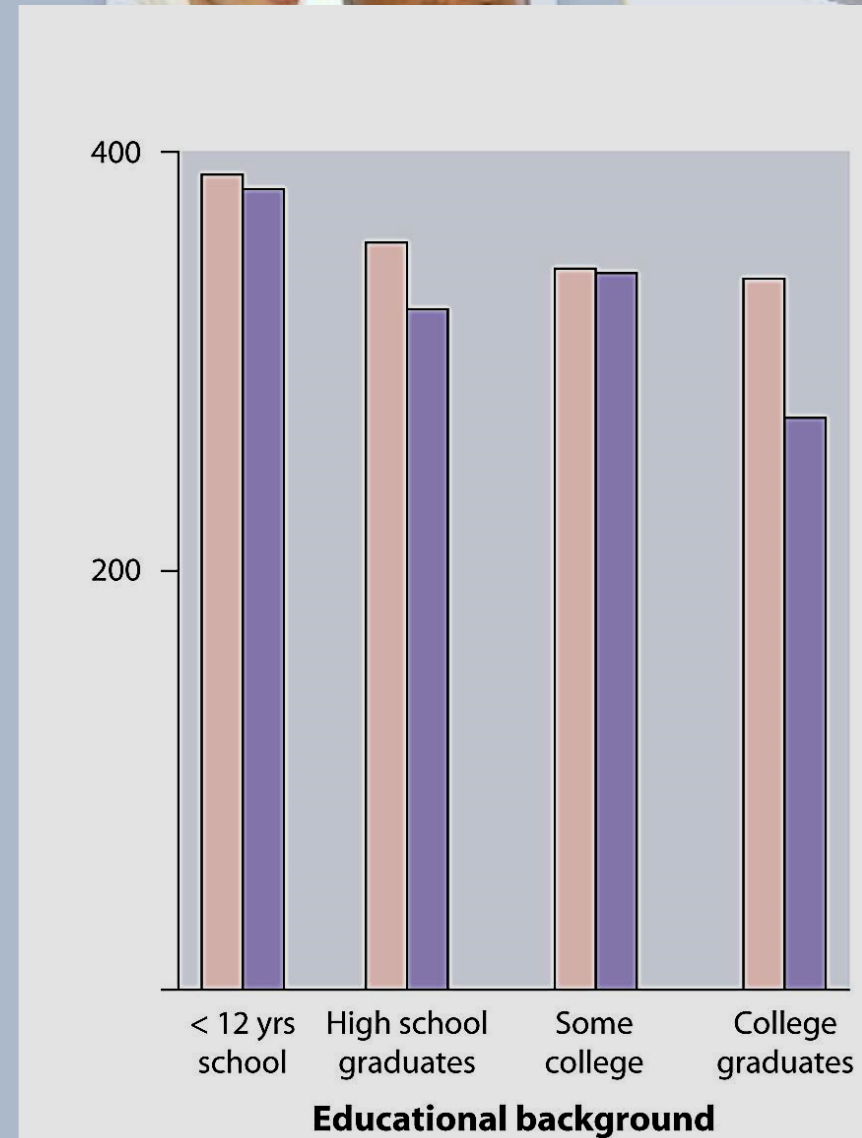
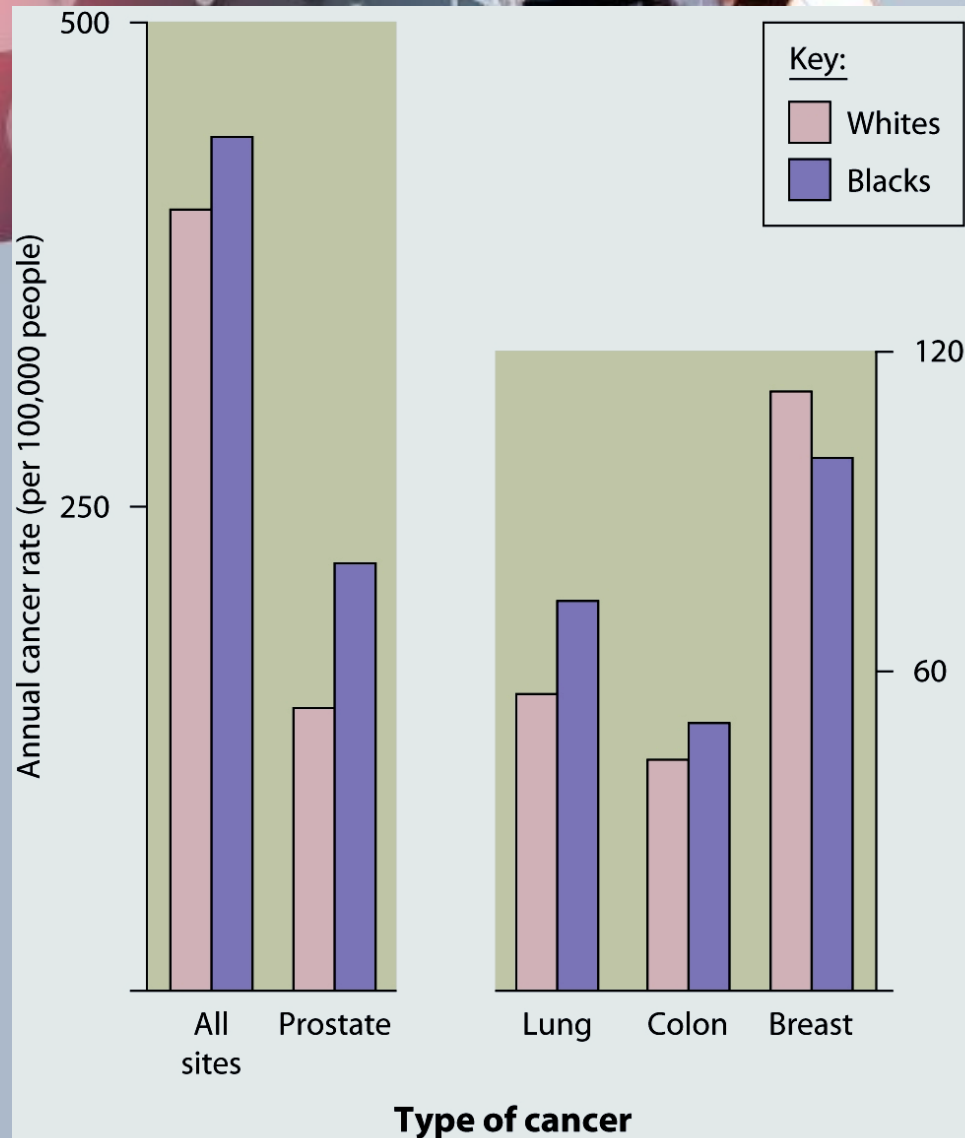
From L. J. Kleinsmith, *Principles of Cancer Biology*.
Copyright (c) 2006 Pearson Benjamin Cummings

Inheritance and Prostate Cancer

- ❑ Hereditary prostate cancer accounts for 5% to 10% of all prostate cancers
- ❑ Men who inherit prostate cancer tend to get the disease at a younger age
- ❑ Tumor grade, symptoms at diagnosis, initial therapy & survival were similar in the hereditary and control groups (Swedish study)



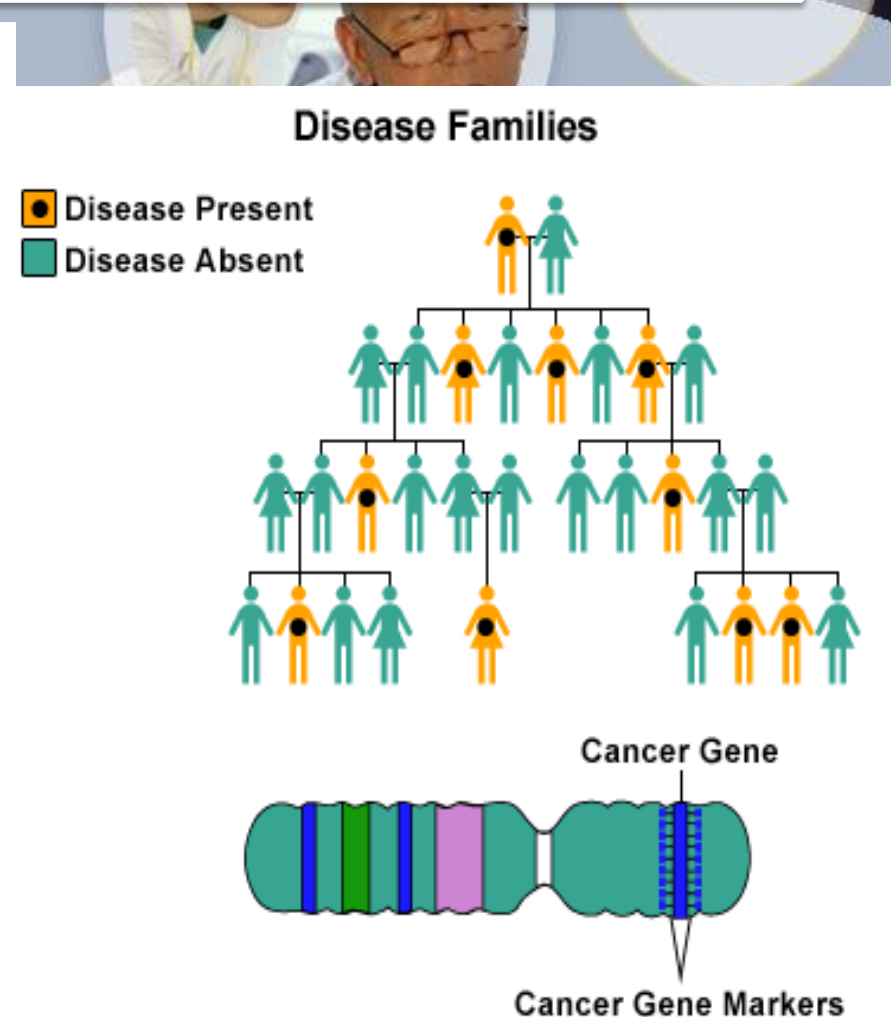
Racial/Educational Differences in Cancer Incidence



From L. J. Kleinsmith, *Principles of Cancer Biology*. Copyright (c) 2006 Pearson Benjamin Cummings.

Possible Benefits of Gene Testing?

- ☐ Allow for a more accurate assessment of cancer risk
- ☐ If positive, doctors can screen earlier for cancers
- ☐ If results are negative, individuals may not have to screen as aggressively
- ☐ Early cancer screening can be offered to other at-risk family members if a mutation is identified
- ☐ No physical risks involved in genetic testing



Possible Risks of Gene Testing?

- ☐ Genetic testing can be emotionally difficult regardless of the results.
- ☐ Emotional stress on relatives who have not had genetic testing (make assumptions about their own genetic status)
- ☐ Health insurance coverage for cancer screening
- ☐ Possibility of employer or insurance provider discrimination based on genetic test results

