

Genes & Cancer

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Biochemistry & Structural Biology

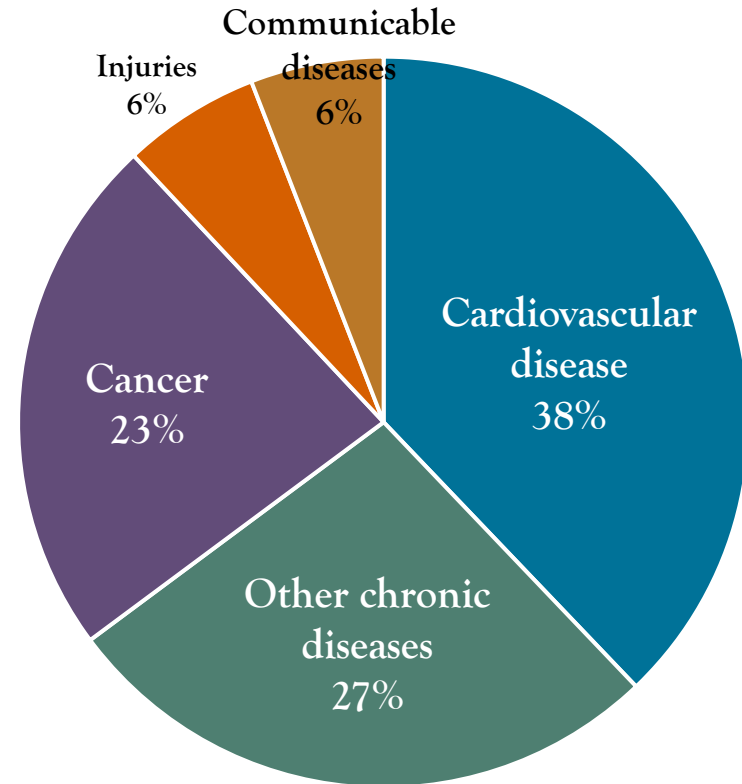
Program Leader

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Cancer is a Leading Cause of Mortality

World Health Organization: In 2009, more than 1,500 people succumbed to cancer in the United States daily

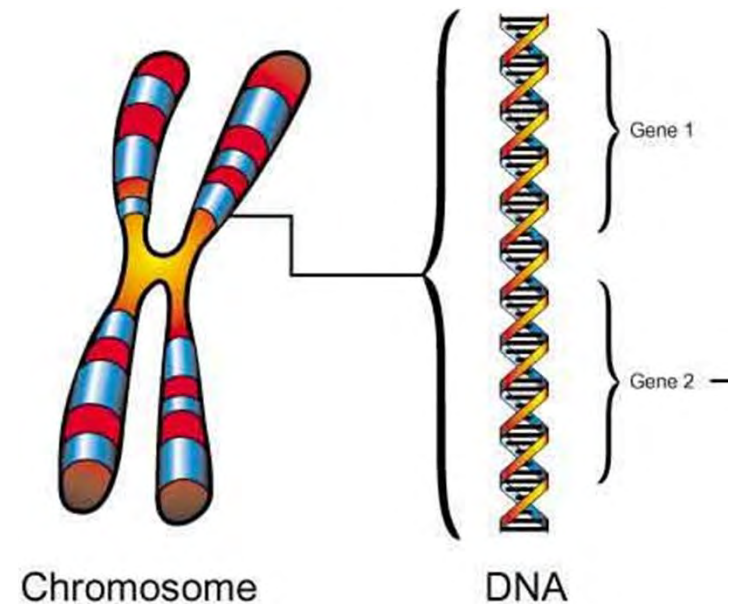


Cancer can be caused by:

- DNA mutations and chromosome rearrangements
from DNA damage & errors when DNA is made
- Viruses & bacteria
- Changes in hormone levels and types

DNA, Genes & Chromosomes

- DNA (has two strands) contains genes (~ 20,000 in humans) and constitutes the genetic blueprint that determines everything from hair color to how tall we are
- DNA is packaged into chromosomes, 23 pairs in humans
- Unrepaired DNA damage can lead to permanent changes (i.e. mutations) in our genetic blueprint and cause disease



DNA damage occurs constantly, in every cell

Damage	Events /cell / day
Single-strand breaks	50,000
Depurination	10,000
Deamination	600
Uracil	
Hypoxanthine	
Oxidation	2,000
8-oxoguanine	
5-hydroxycytosine	
Thymine glycol	
Hydroxymethyl uracil	
Alkylation	5,000
3-methyladenine	
O ⁶ -methylguanine	
Interstrand cross-link	10
Double-strand breaks	10

DNA damage occurs constantly, yet mutations & chromosome aberrations arise infrequently – why?

Our genetic material is kept intact by DNA repair!

Essence of DNA Repair & Cancer Genetics

Much of what we know about how DNA repair works has originated from examining cells from cancer patients who are deficient in the repair process, and also mutant form of simple organisms such as bacteria, yeasts, and the fruit fly.

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Xeroderma Pigmentosum (XP)

- Inherited disorder (because of gene defects)
- Extreme sensitivity to sunlight, because of an inability to remove sunlight-induced DNA damage
- 2000 times more susceptible to **skin cancer**



Photo from Milota, DNA Repair (2011)

Name the movie and describe
the plot involving
Nicole Kidman's two
children



The Others

Grace's two children have to stay in the dark as they have **Xeroderma Pigmentosum**

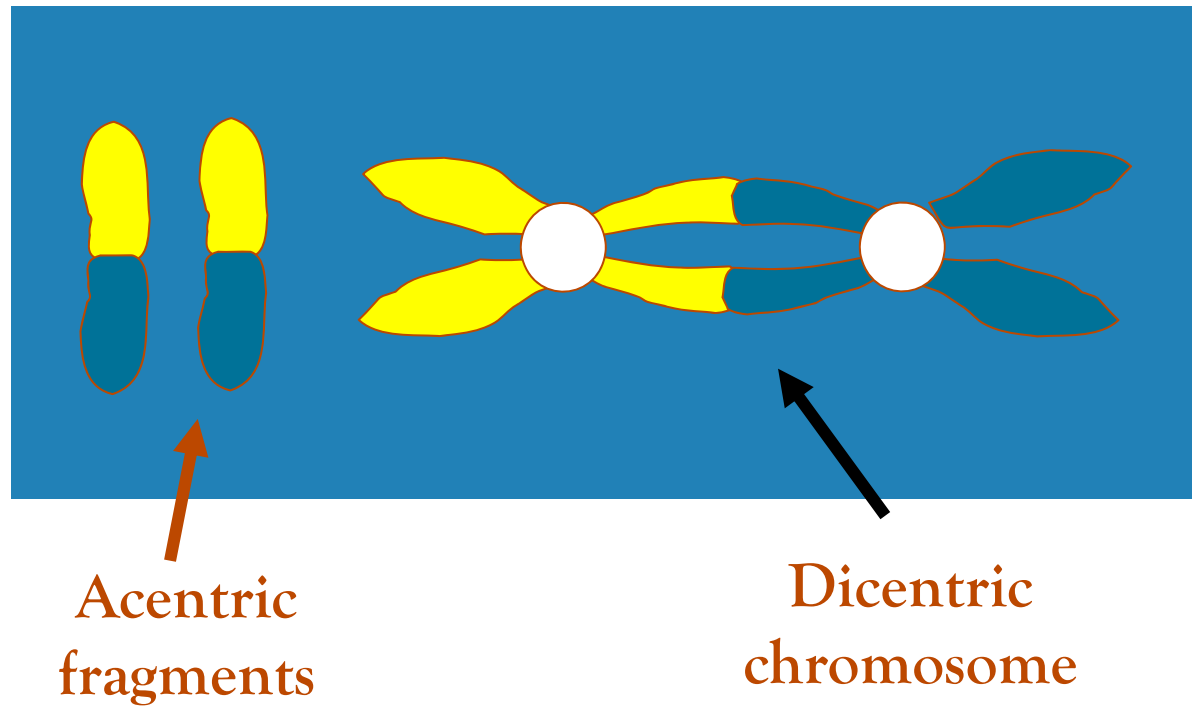


Xeroderma pigmentosum is very rare, but **breast and ovarian cancers** caused by mutations in **genes that help fix broken DNA** are quite common

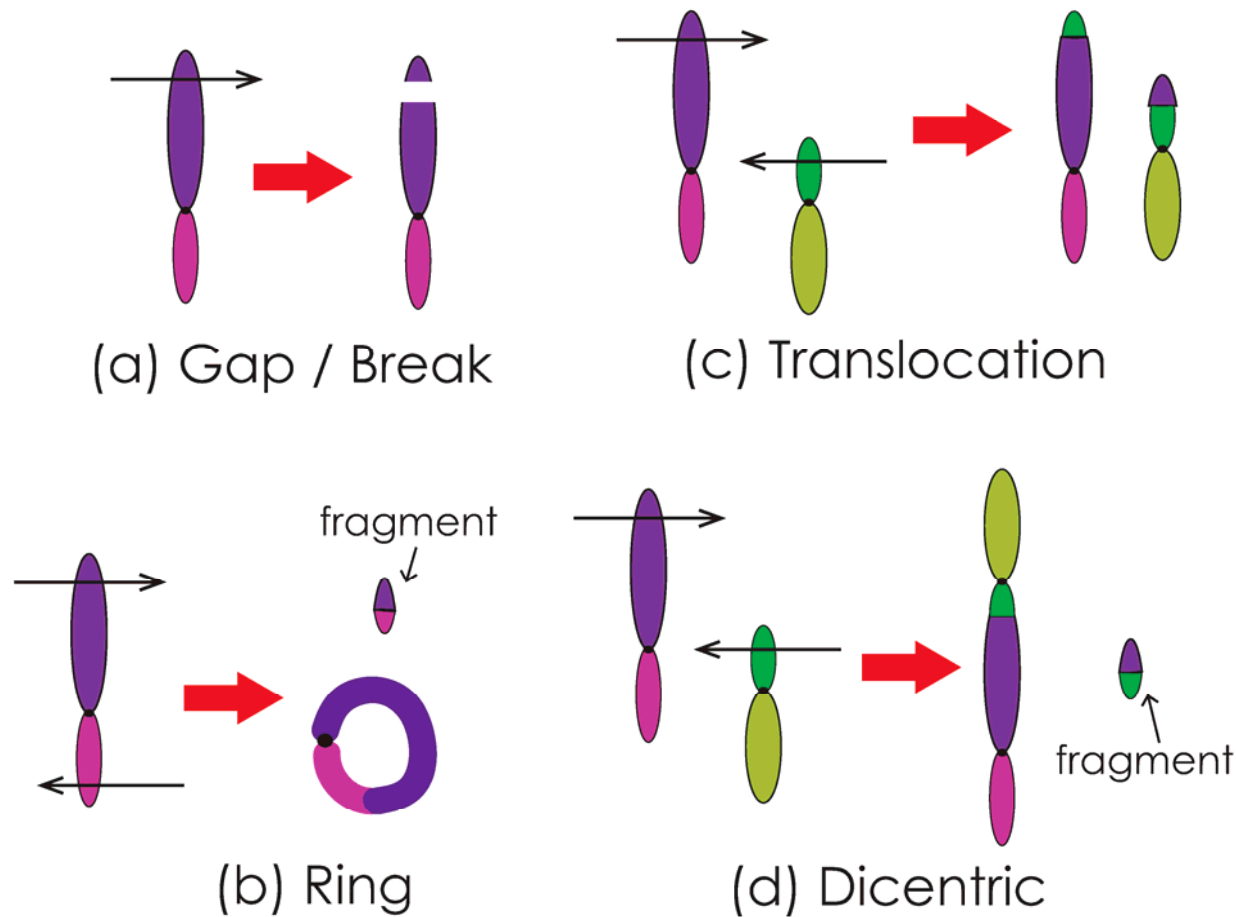
DNA breaks are highly toxic lesions

Chromosome rearrangements and loss can result
from failure to remove DNA breaks

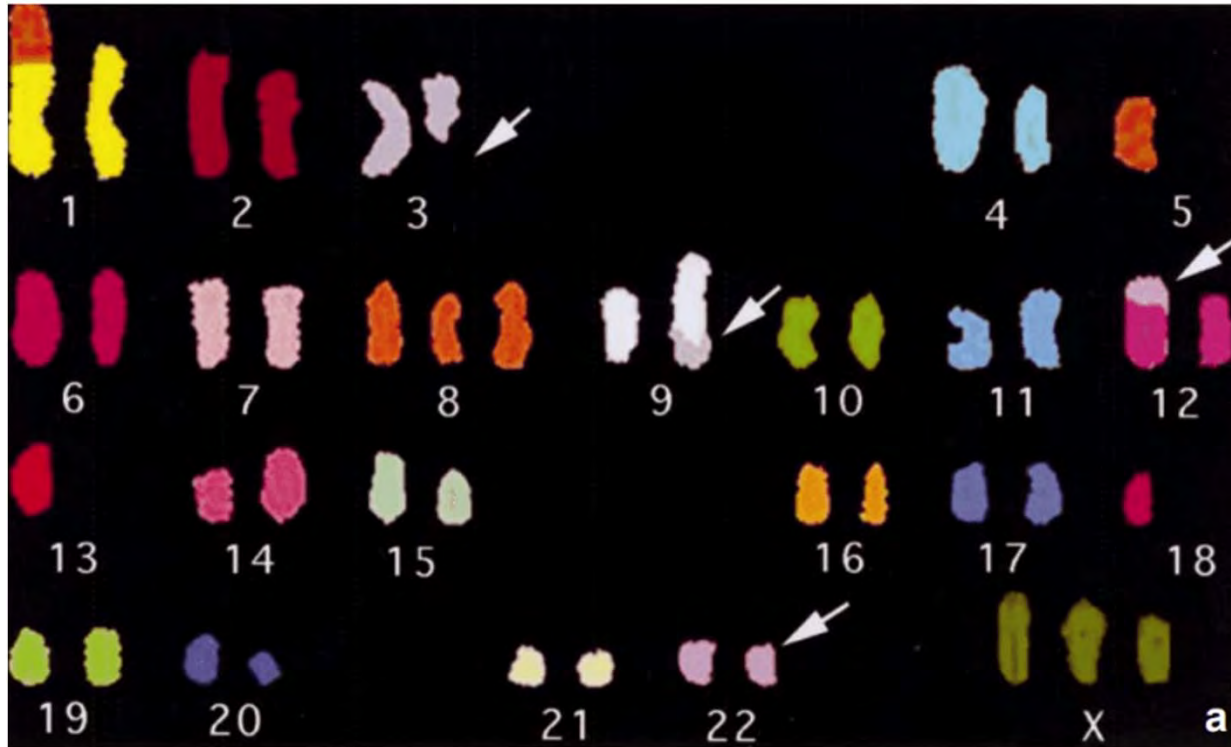
Rearrangements Induced by DNA Breaks



Chromosome Aberrations Induced by DNA Breaks



Abnormal Karyotype of Cancer



Karyotype - number and appearance of chromosomes
Humans have 23 pairs of chromosomes



Mary Claire King, Ph.D.
(University of Washington, Seattle)

Discoverer, Breast Cancer Gene 1
(BRCA1)

Huffpost: The week my husband left and
my house was burgled I secured a grant to
begin the project that became BRCA1

BRCA Genes in Cancer Etiology

- **BRCA1 & BRCA2 mutations:** Familial Breast & Ovarian Cancers, with **lifetime risk to 80% and 60%, respectively.**
- Also relevant for pathogenesis of prostate, pancreatic, brain and pediatric cancers.
- ***BRCA1 & BRCA2 genes function in DNA break repair.**
- *Tumors often exhibit **BRCA-ness**, i.e. they are deficient in DNA break repair.

BRCA Genes and Cancer



"My doctors estimated that I had an 87% risk of breast cancer and a 50% risk of ovarian cancer."

Mastectomy & oophorectomy to alleviate cancer risk

SCIENCE, 1994, 265:1241-3. Patrick Sung

Catalysis of ATP-Dependent Homologous DNA Pairing
and Strand Exchange by RAD51 Protein.

This study identified RAD51 as the “Recombinase” enzyme
responsible for DNA break repair.

NATURE, 2017, 550:360-5. Wilson Zhao, Sung, et al

BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing.

This study discovers how BRCA1 enhances the activity of RAD51. This attribute could be targeted in cancer therapy.

*Many cancer drugs work by targeting DNA or DNA repair

Objectives at UT Health San Antonio and UT Health San Antonio MD Anderson Cancer Center

Elucidate how BRCA1, BRCA2, RAD51, and their partners mediate DNA repair

Define how gene mutations lead to breast, ovarian, and other cancers and cause acquired drug resistance

Work with basic scientists, medicinal chemists, and clinicians to develop cutting-edge cancer therapeutics

Train cancer researchers through post-doctoral, graduate and college programs and high school student mentorship