Radiation-induced DNA damage

We are exposed to radiation everywhere in the world

Current industry and medicine are largely supported by radiation

Benefit and/or risk ?

Specific issues of radiation in Japan

Disaster of atomic bombs in Hiroshima and Nagasaki

Frequent use of X-ray in diagnostic medicine

Infrequent application of therapeutic radiotherapy

Effects of radiation on humans at molecular levels

Indirect effects

Caused by free radicals

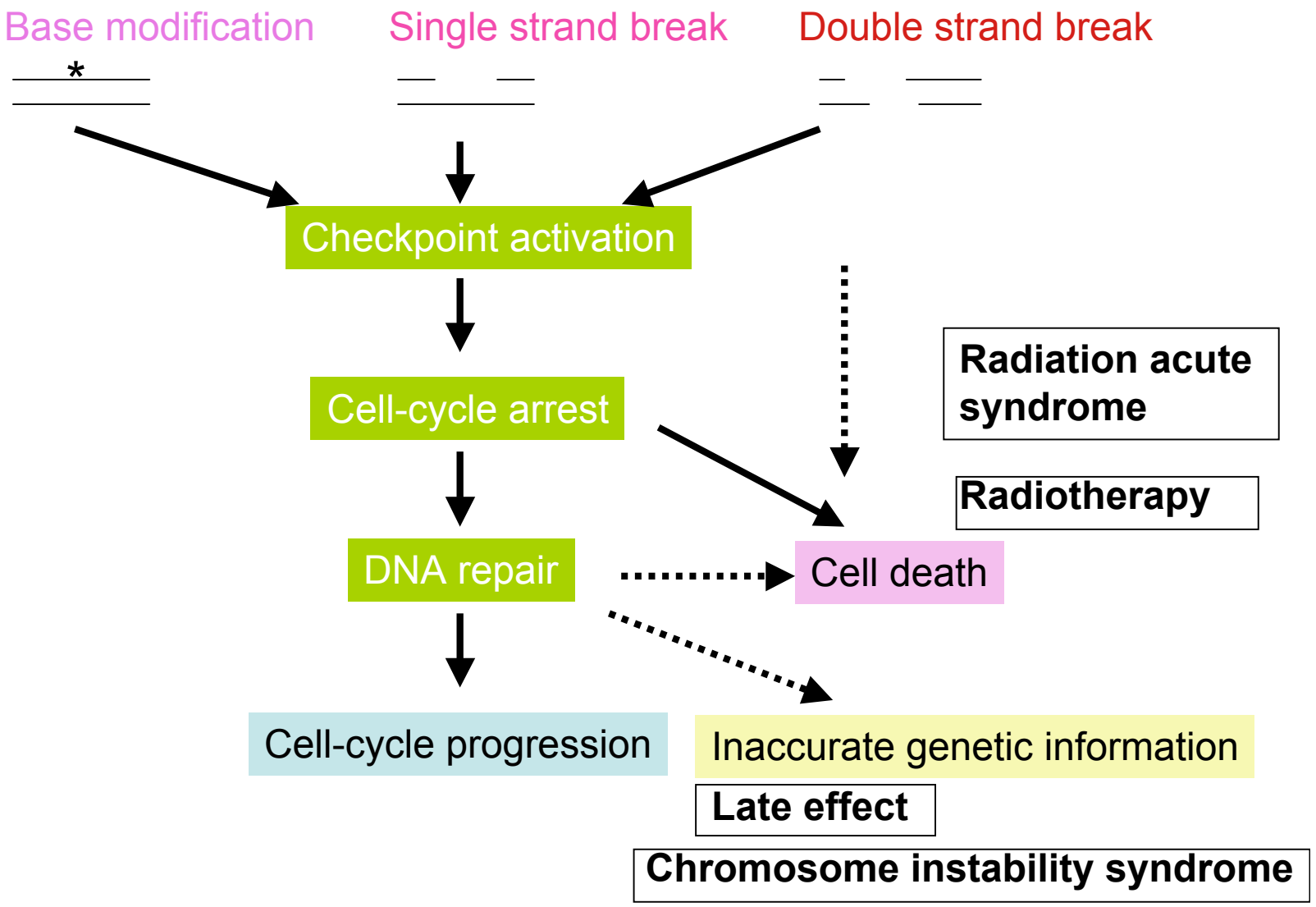
→ Reversible

Direct effects

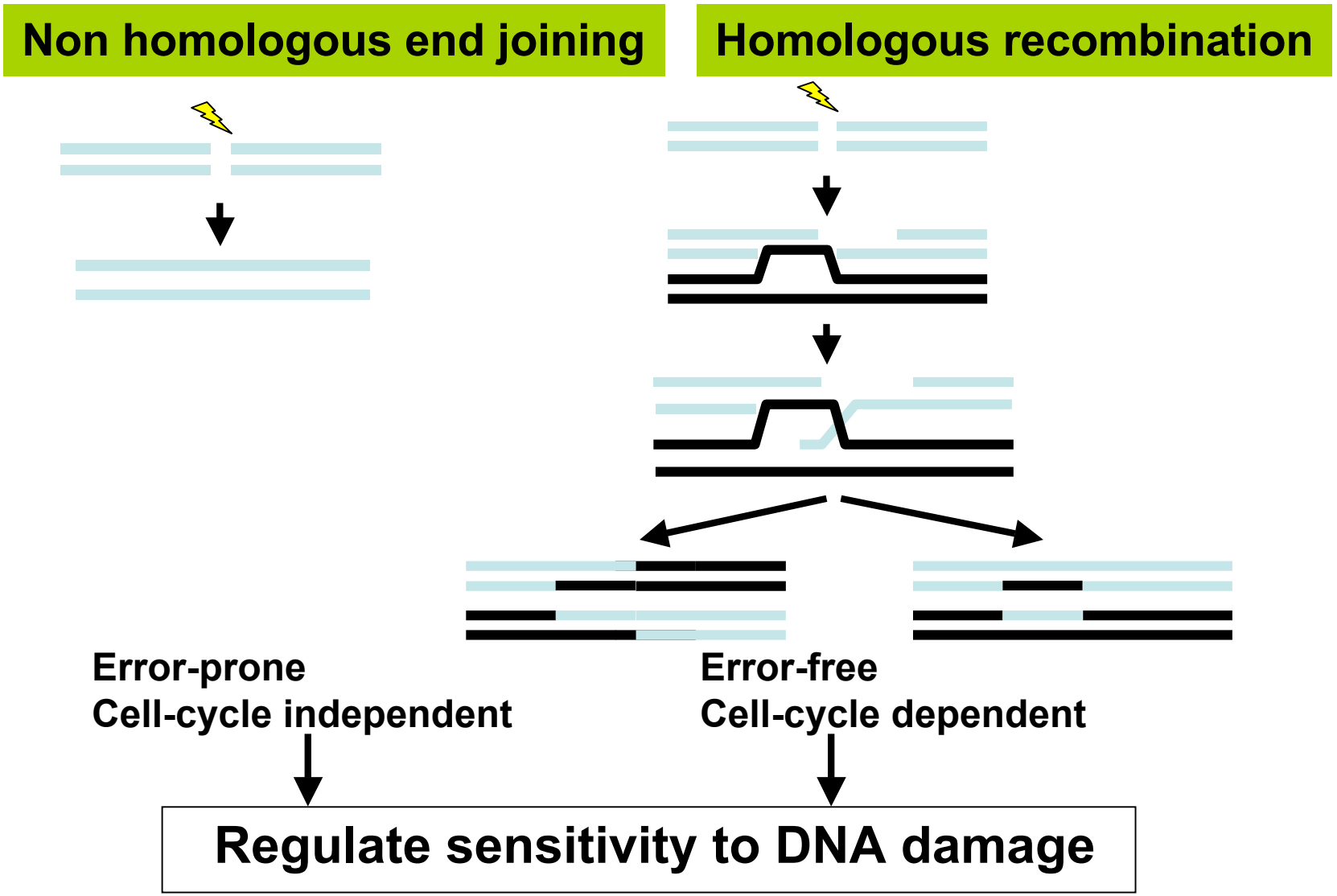
Caused by DNA damage or modification

→ Often irreversible

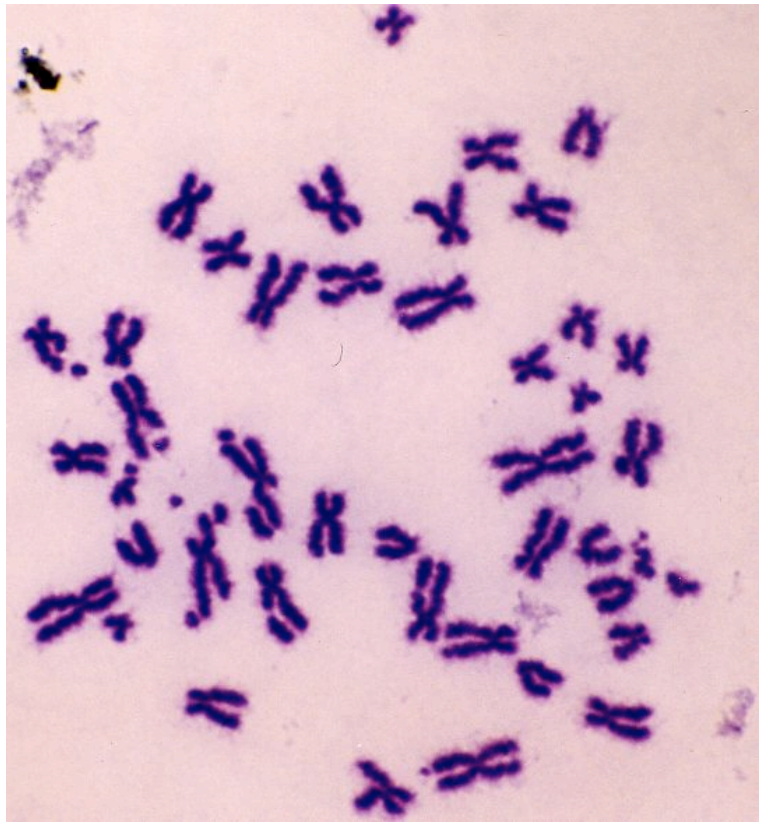
Direct effects of radiation



Two major pathways of double strand breaks

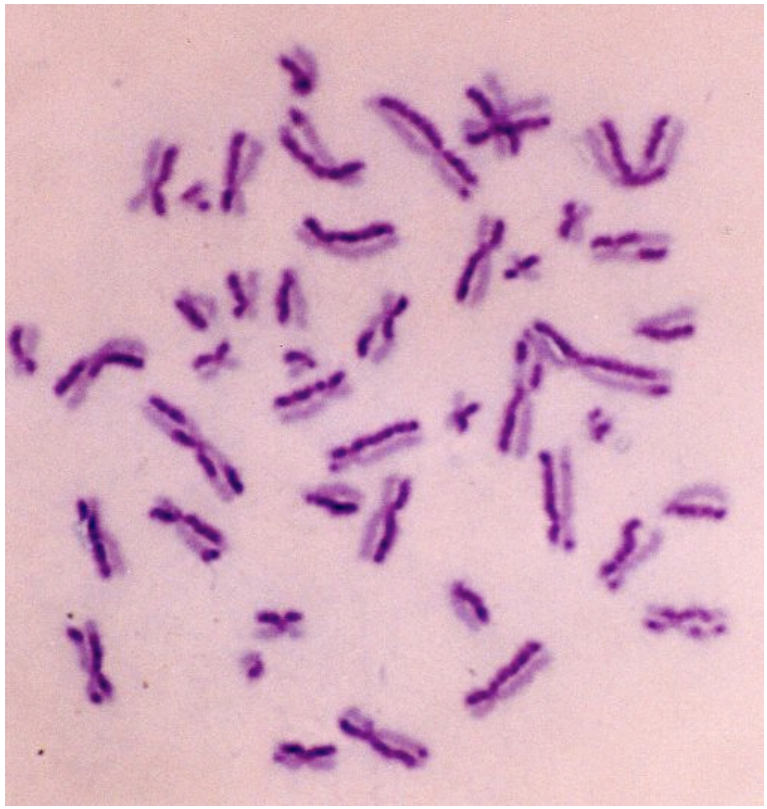


Homologous recombination is required for chromosome integrity



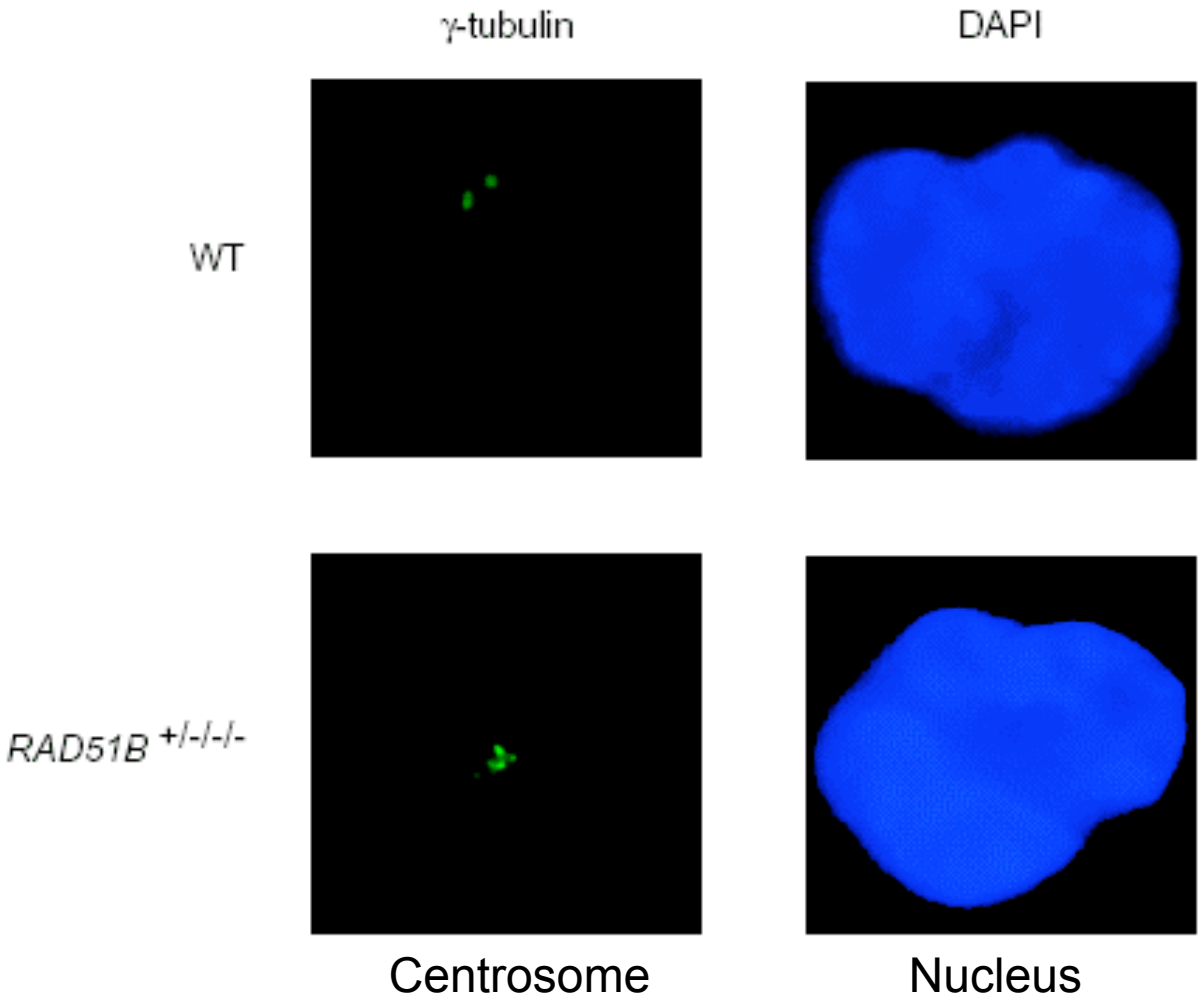
Chromatid breaks are increased in cells with defective homologous recombination

Sister chromatid exchange



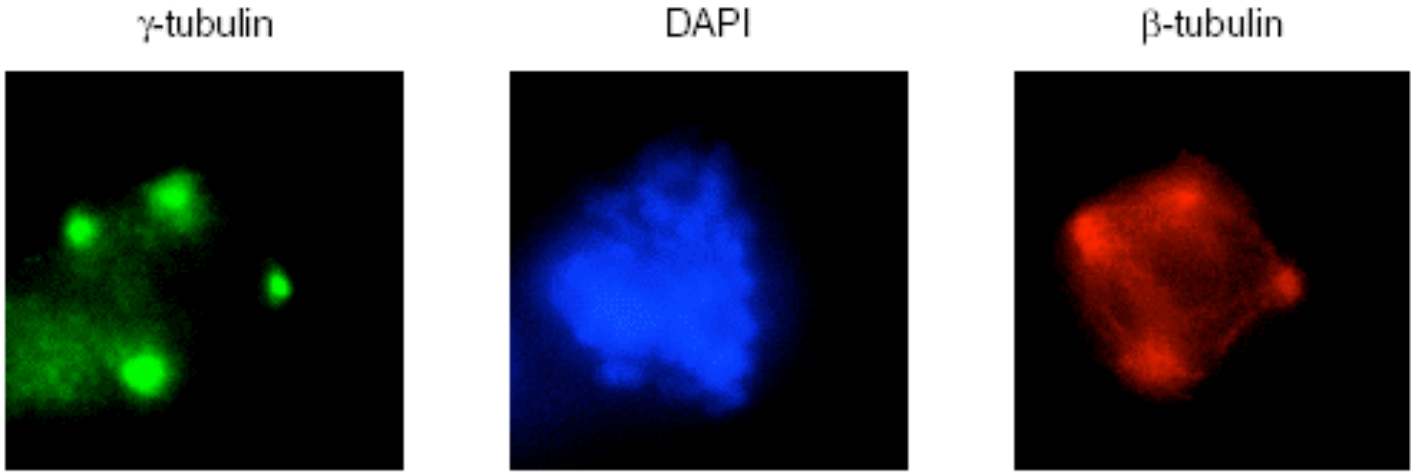
Sister chromatid exchange is required for the repair of double strand breaks

Centrosome fragmentation



Centrosomes tend to fragment in cells deficient in homologous recombination

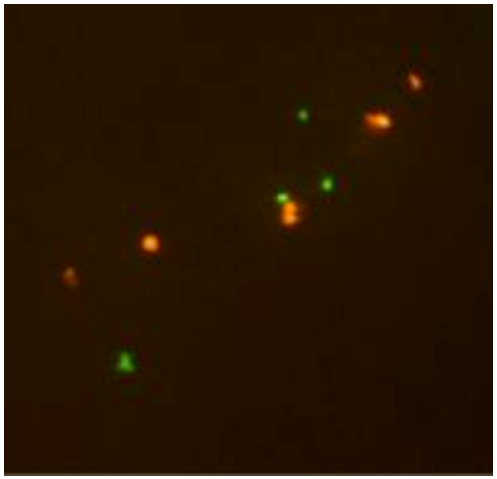
Multipolar spindle formation



Multipolar spindle formation is observed in cells with defective homologous recombination

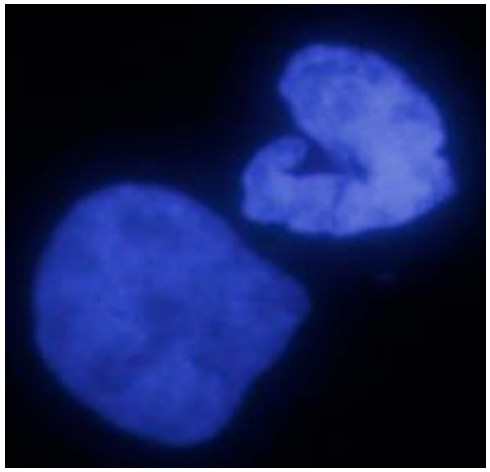
Aneuploidy- a cell with abnormal chromosome numbers

FISH



Centrosome

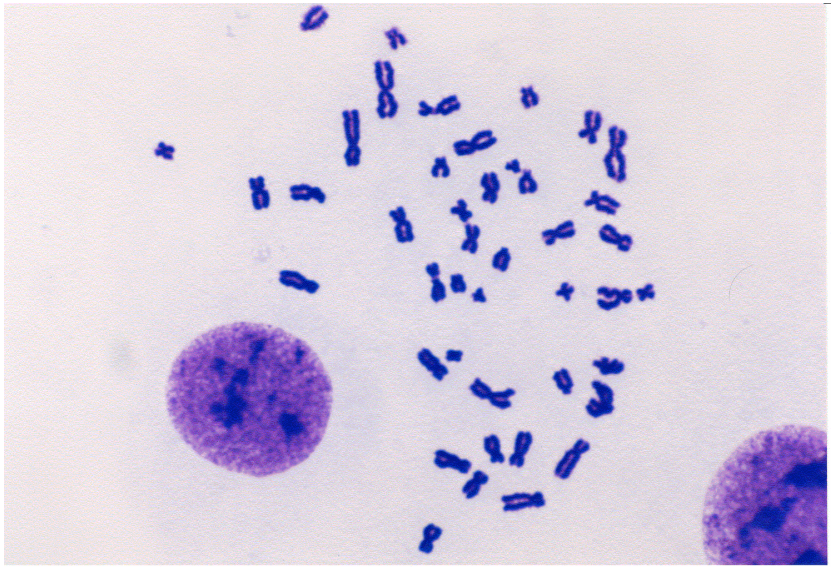
DAPI



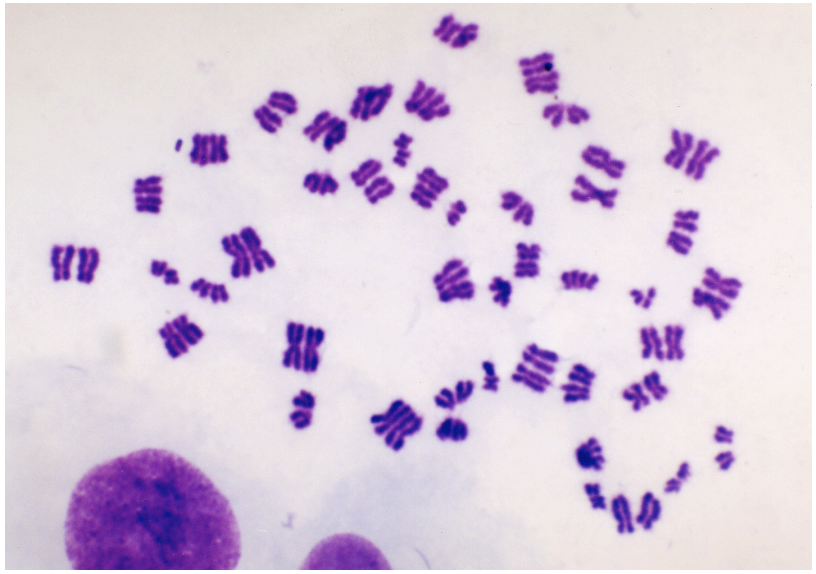
Nucleus

Centrosome fragmentation and multipolar spindles often result in aneuploidy

Chromosome duplication



Diploidy



Tetraploidy

An increase in tetraploidy is observed in cells with defective homologous recombination

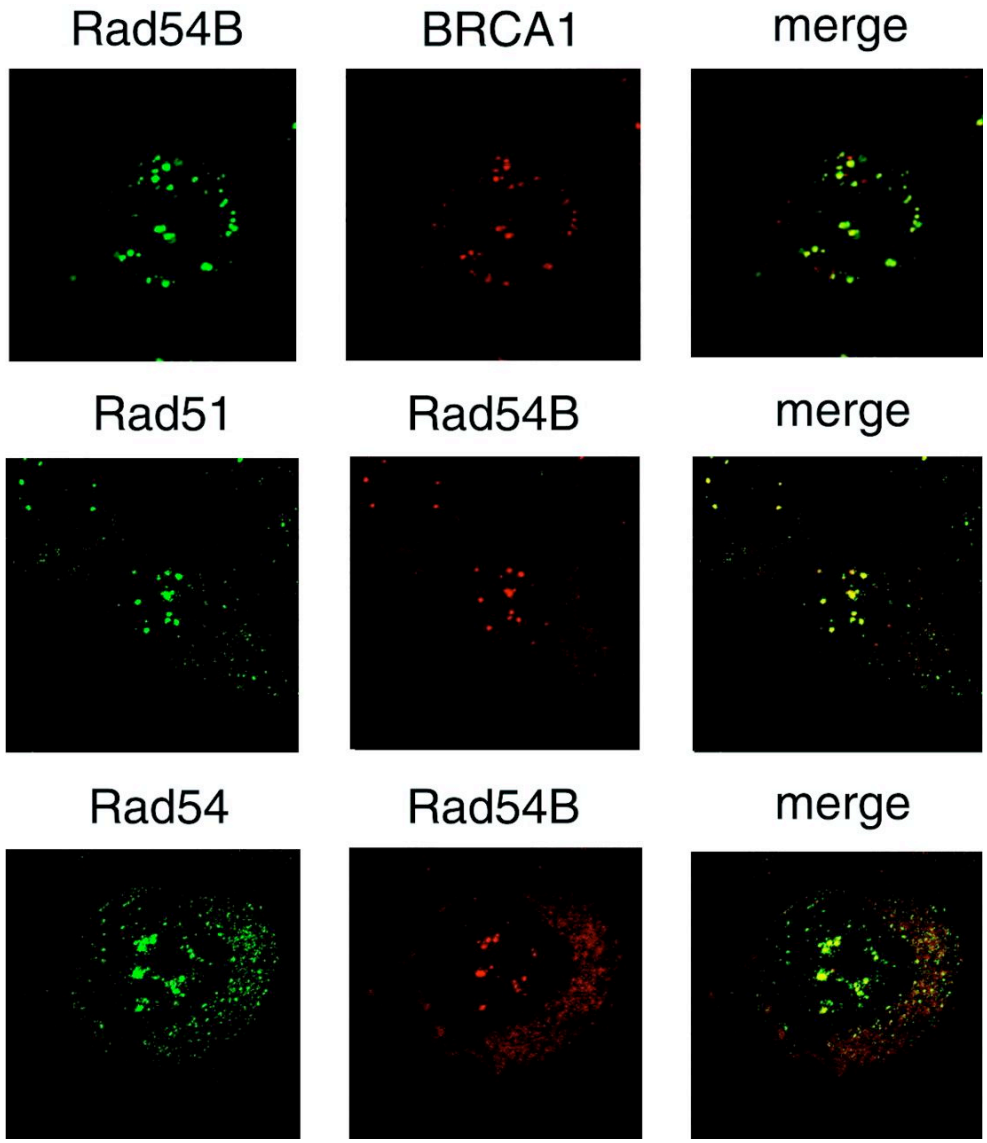
Failure to repair double strand breaks affects chromosome integrity

DNA damage induced by radiation, unless repaired properly, causes chromosome aberrations, leading to cell death or generation of abnormal cells harboring incorrect genetic information

Clinical manifestations of chromosome instability syndrome

	Ataxia-telangiectasia	Nijmegen syndrome	Bloom syndrome	Werner syndrome	Rothmund-Thomson syndrome	Fanconi anemia
Cancer	O	O	O	O	O	O
Ataxia	O	-	-	-	-	-
Developmental delay	O	O	O	O	O	O
Premature aging	-	-	-	O	O	-
Immunodeficiency	O	O	O	-	-	-
Hematological disorder	-	-	-	-	-	O
Skin symptoms	O	O	O	O	O	O
Telangiectasia	O	-	O	-	O	-

Protein localization in the nucleus after irradiation



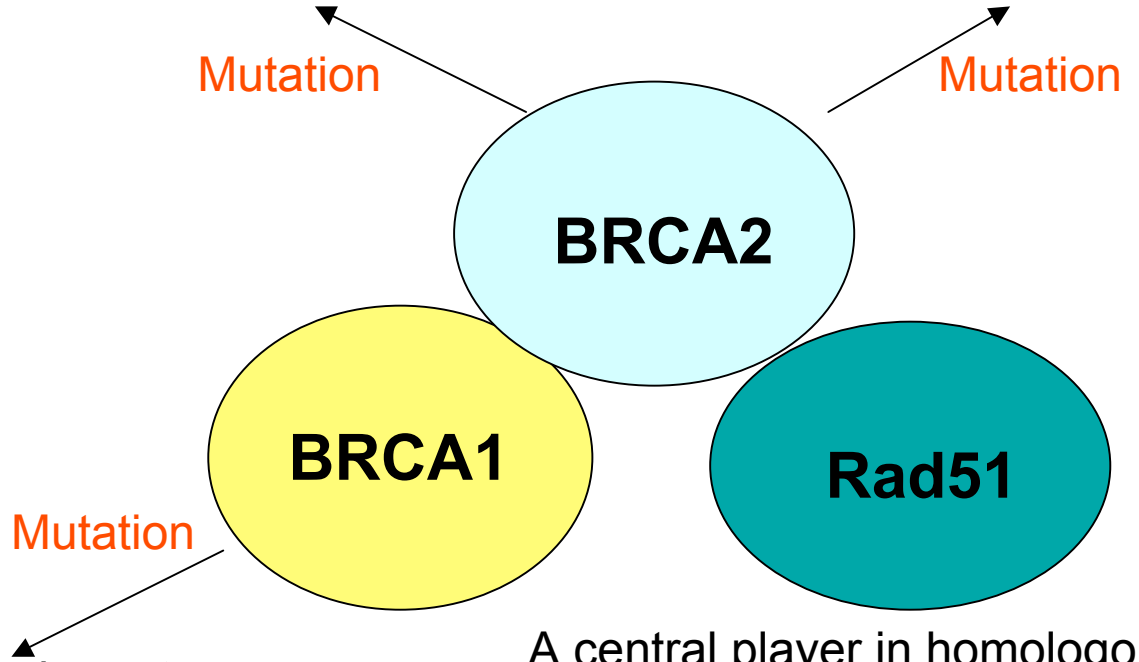
Rad51, Rad54 and Rad54B are involved in homologous recombination

BRCA1 mutation is responsible for hereditary breast and ovarian cancers

A protein complex inhibiting breast and ovarian cancers

Hereditary breast cancers
Ovarian cancers

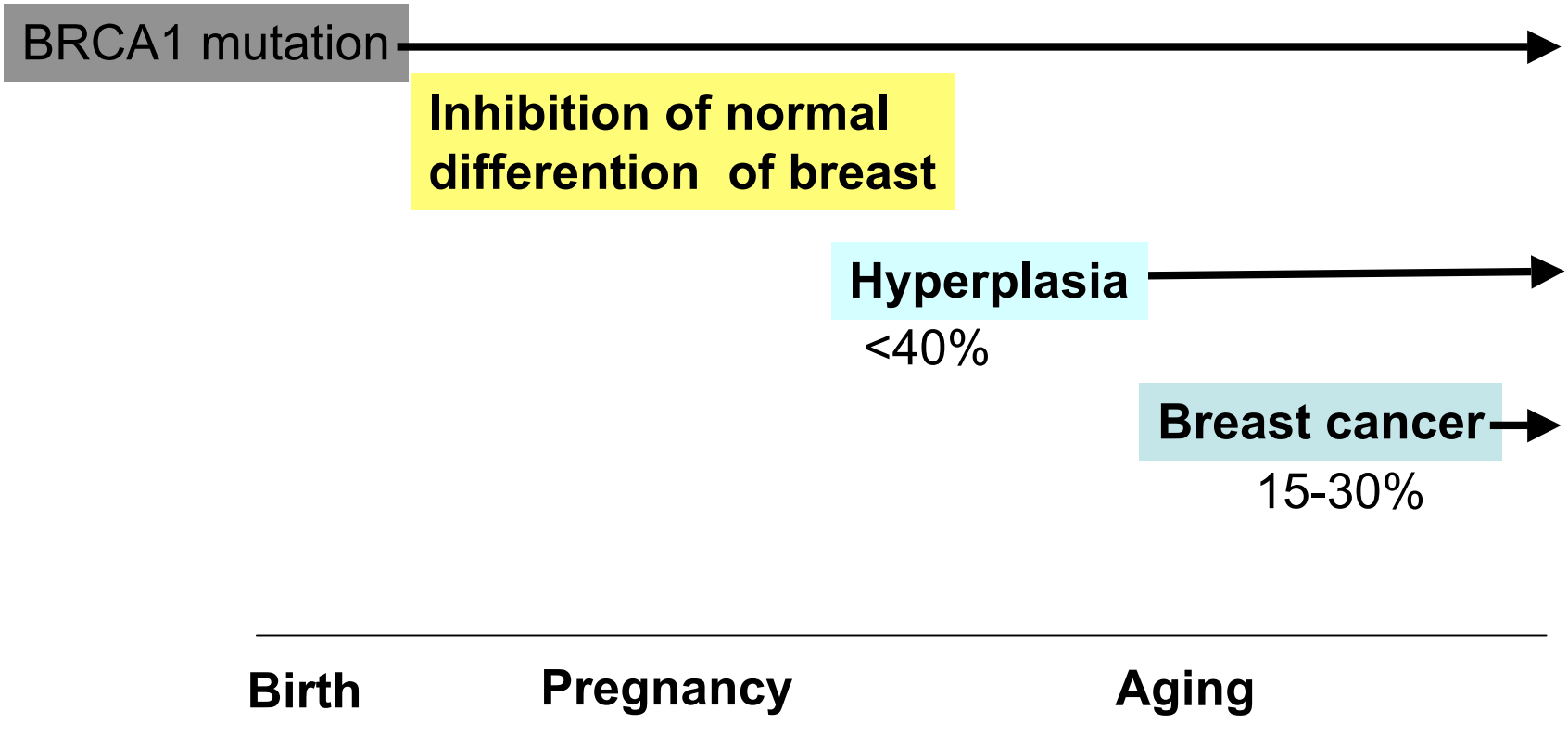
Fanconi anemia
(characterized by developmental abnormality and cancer predisposition)



Hereditary breast cancers
Sporadic breast cancers
Ovarian cancers

A central player in homologous recombination

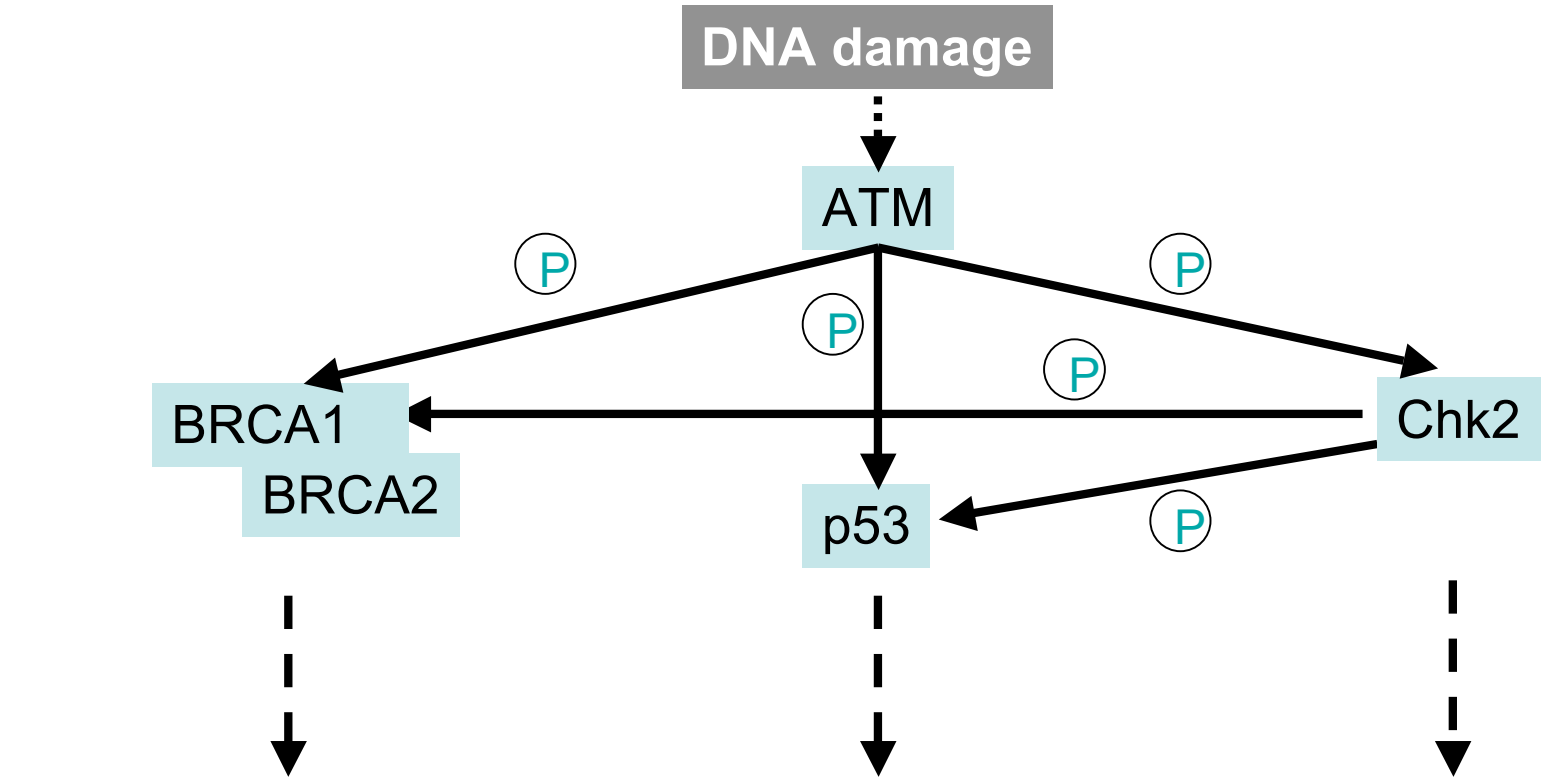
A mouse model of hereditary breast cancers



BRCA1 mutation alone does not lead to carcinogenesis

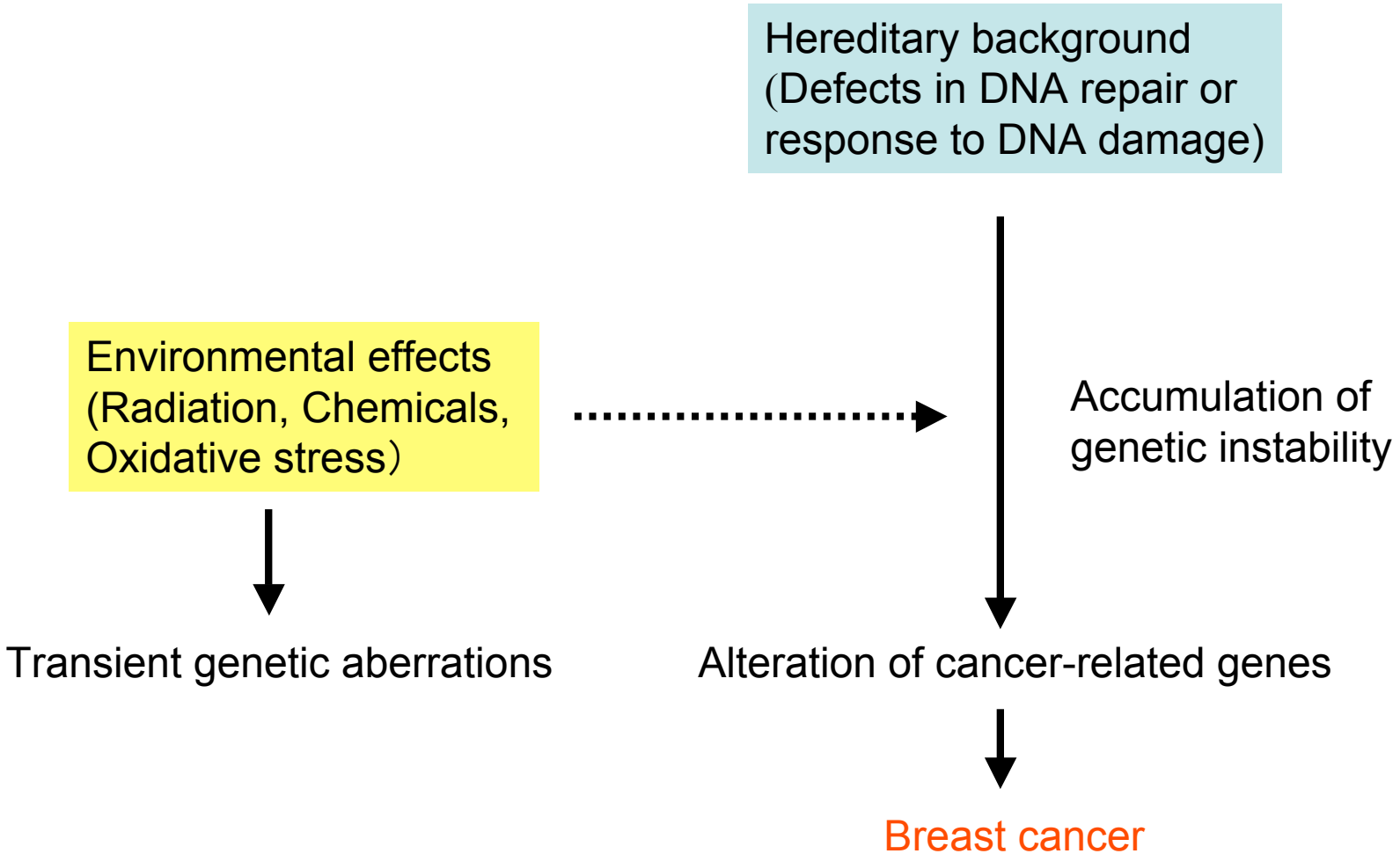
Cancer formation may require accumulation of genetic instability

Genetic background affecting breast cancer risks

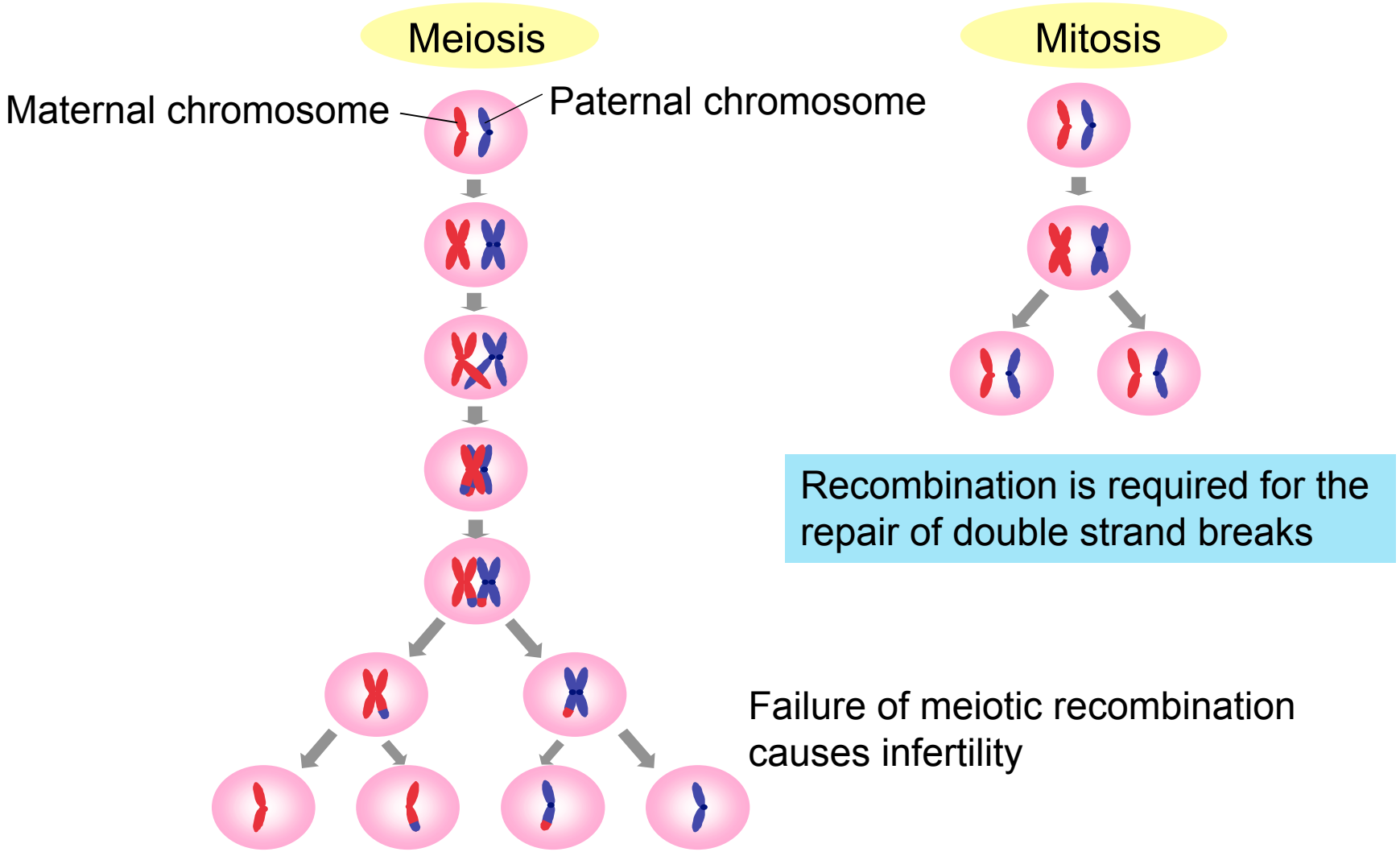


P: phosphorylation

Complex pathways leading to breast cancers



Meiotic recombination and mitotic recombination

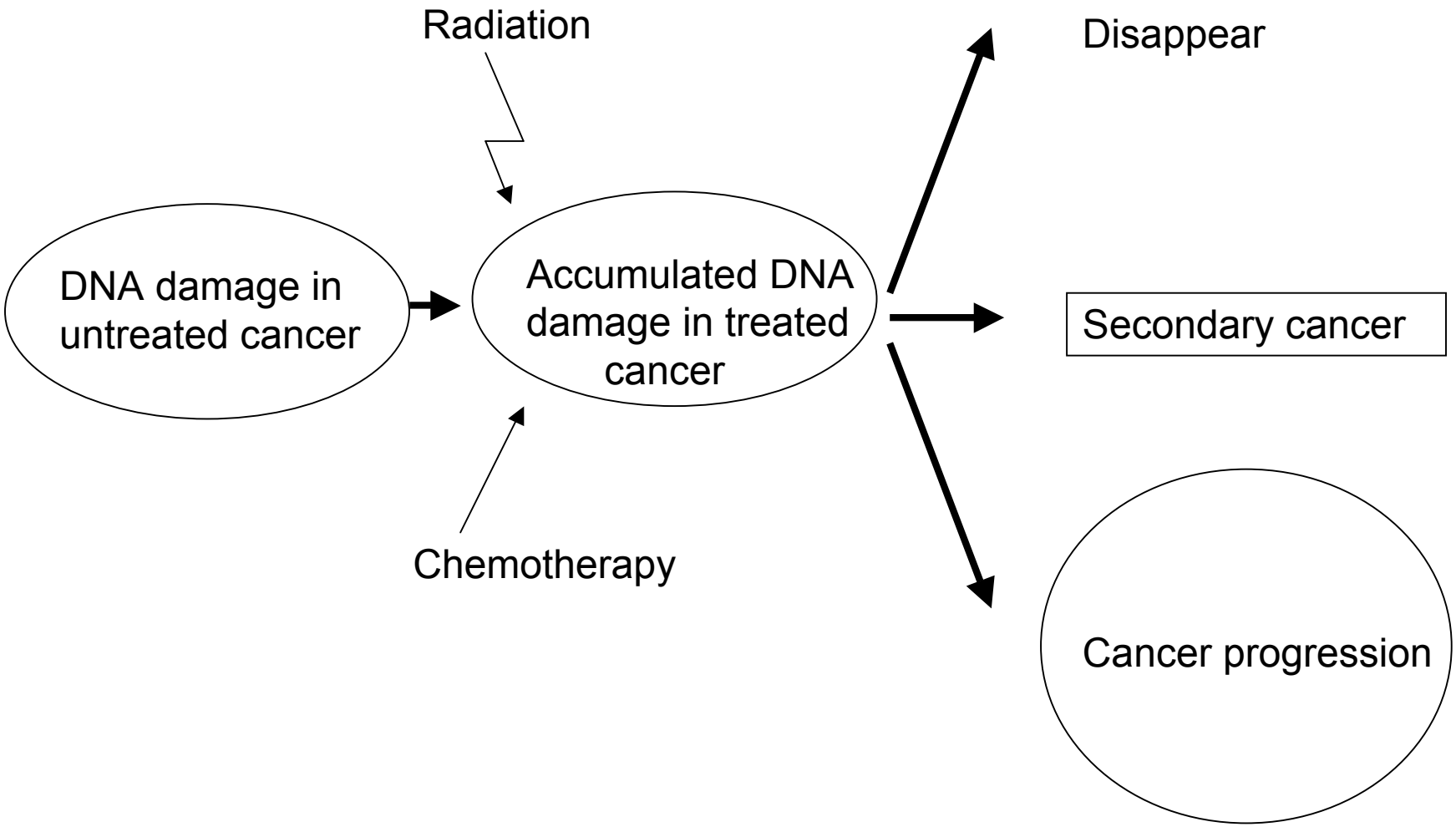


Recombination is required for the repair of double strand breaks

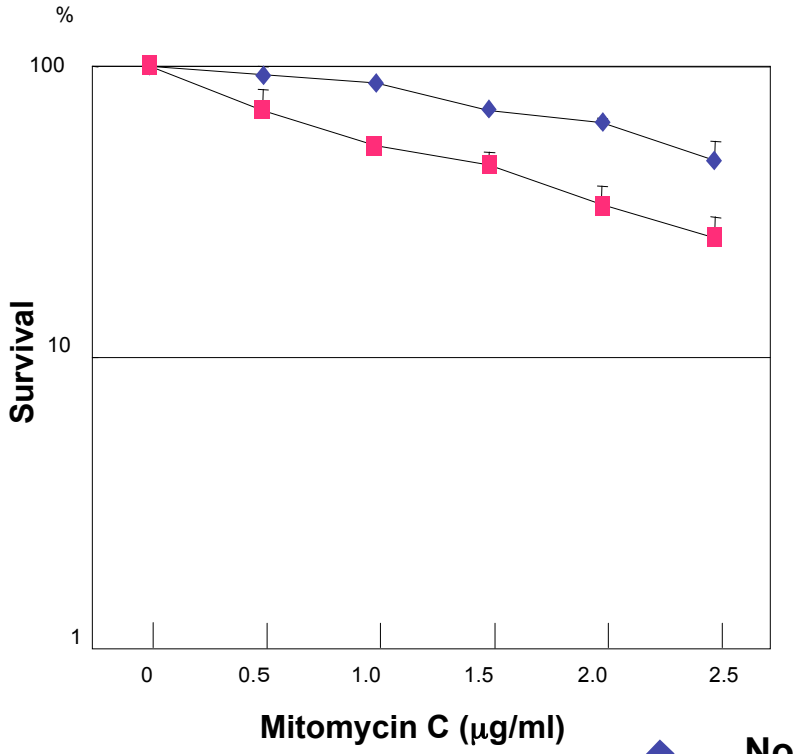
Failure of meiotic recombination causes infertility

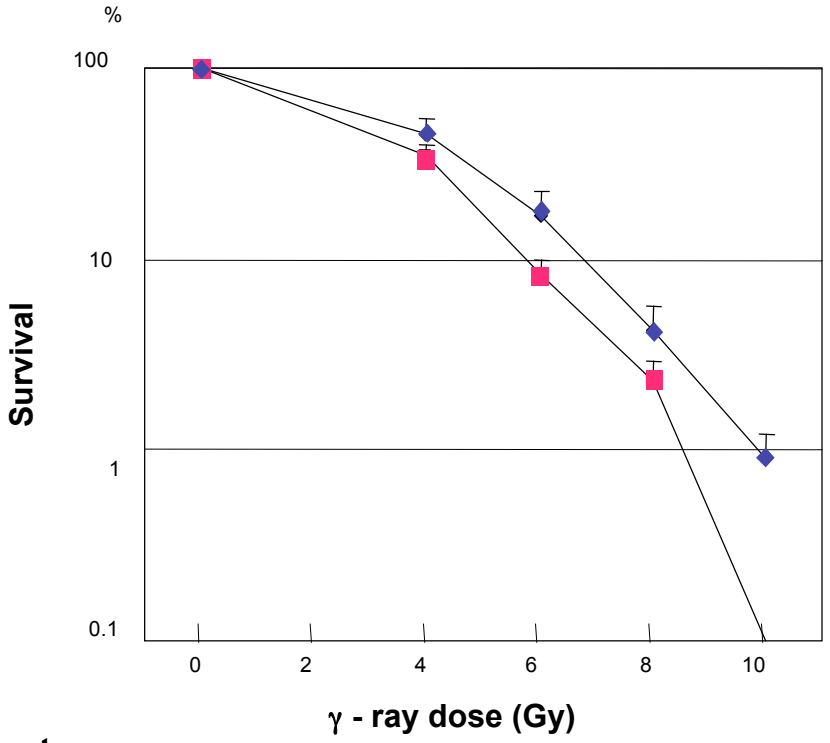
Recombination is required for generation of genetic diversity

DNA damage associated with cancer therapy



Targeting a repair protein in cancer therapy



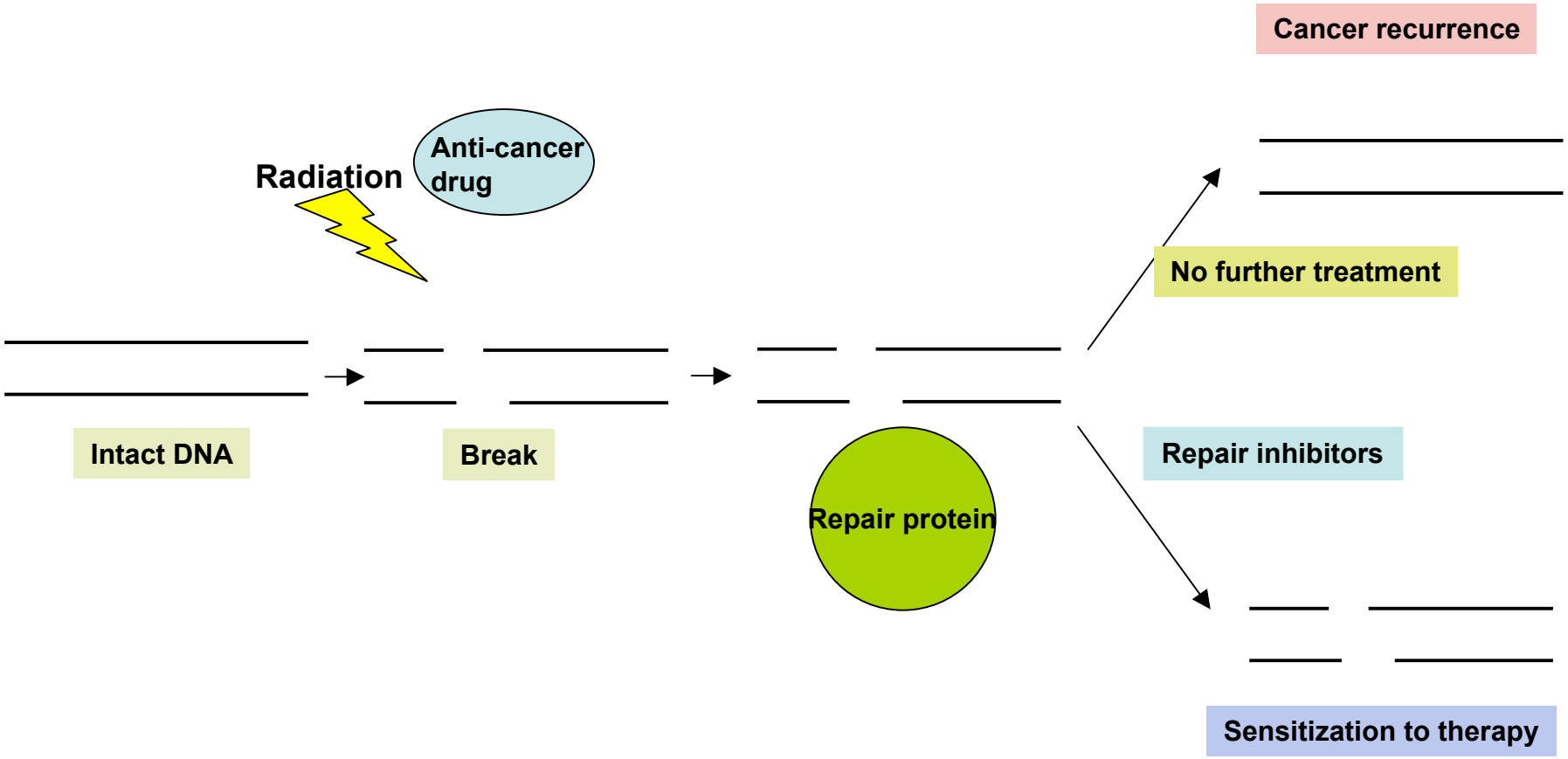


No treatment

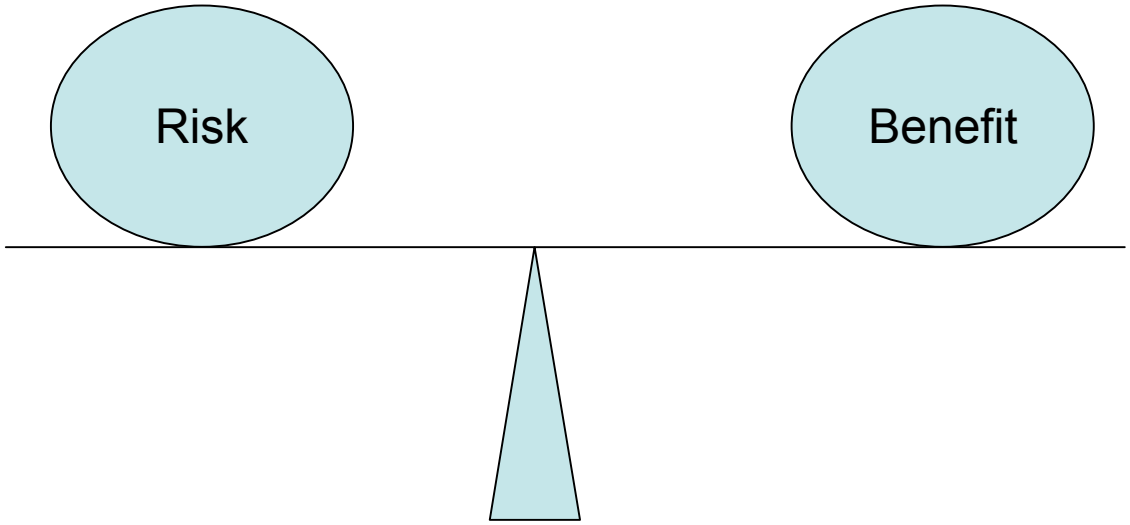
Inhibition of a repair protein

Fibrosarcoma cells that are resistant to therapy become sensitive to therapy by inhibition of a repair protein

A novel strategy of cancer treatment



Risk and benefit of DNA damage



A balance depends on situations and genetic backgrounds

Novel Approach of cancer therapy

Targeted therapy

Inhibitors of molecules expressed specifically in cancer cells are used

Anti-angiogenesis antibody or small molecule
Anti-tyrosine kinase antibody or small molecule

Individualized chemotherapy

Patients with markers predicting good response benefit from the corresponding therapy

Response can be predicated before treatment