

How Does DNA Damage and DNA Repair Influence Breast Cancer?



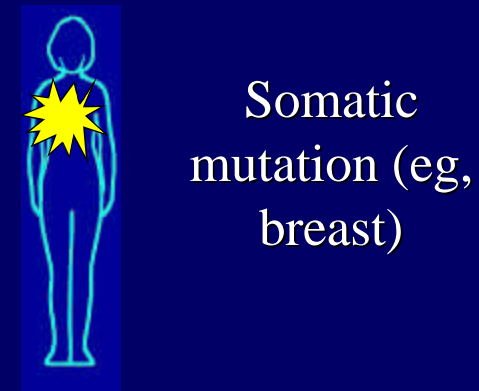
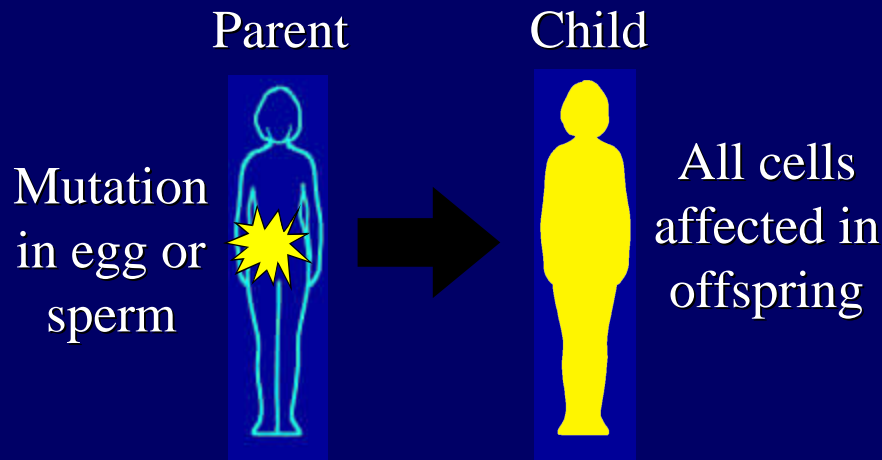
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Cancer Arises From Gene Mutations

Germline mutations

Somatic mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

- Occur in nongermline tissues
- Are nonheritable

Genes Associated With Cancer Predisposition

Tumor suppressor genes

- The cell's brakes for tumor growth
- Cancer arises when both brakes fail

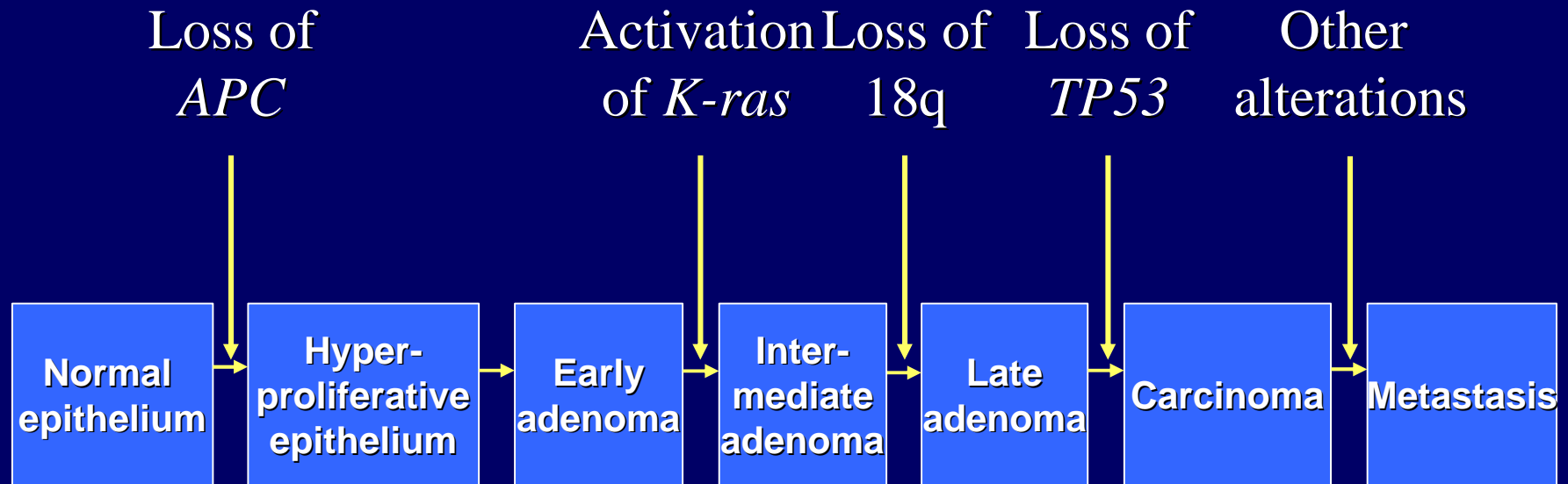
Oncogenes

- Accelerates cell division
- Cancer arises when stuck in "on" mode

DNA damage-response genes

- The repair mechanics for DNA
- Cancer arises when both genes fail, speeding the accumulation of mutations in other critical genes

Multi-Step Carcinogenesis (eg, Colon Cancer)



Adapted from Fearon ER. *Cell* 61:759, 1990

Types of Endogenous DNA Damage

- **Spontaneous Base Loss** - apurinic/apyrimidinic (AP) site
100's - 1000's per day per haploid genome
- **Base Deamination** - cytosine to uracil
100's per day
- **Base Modification due to Reactive Oxygen Species**
Thymine glycols, 8-oxoguanine, etc.
- **Base-Pair Mismatches and IDLs** due to replication errors

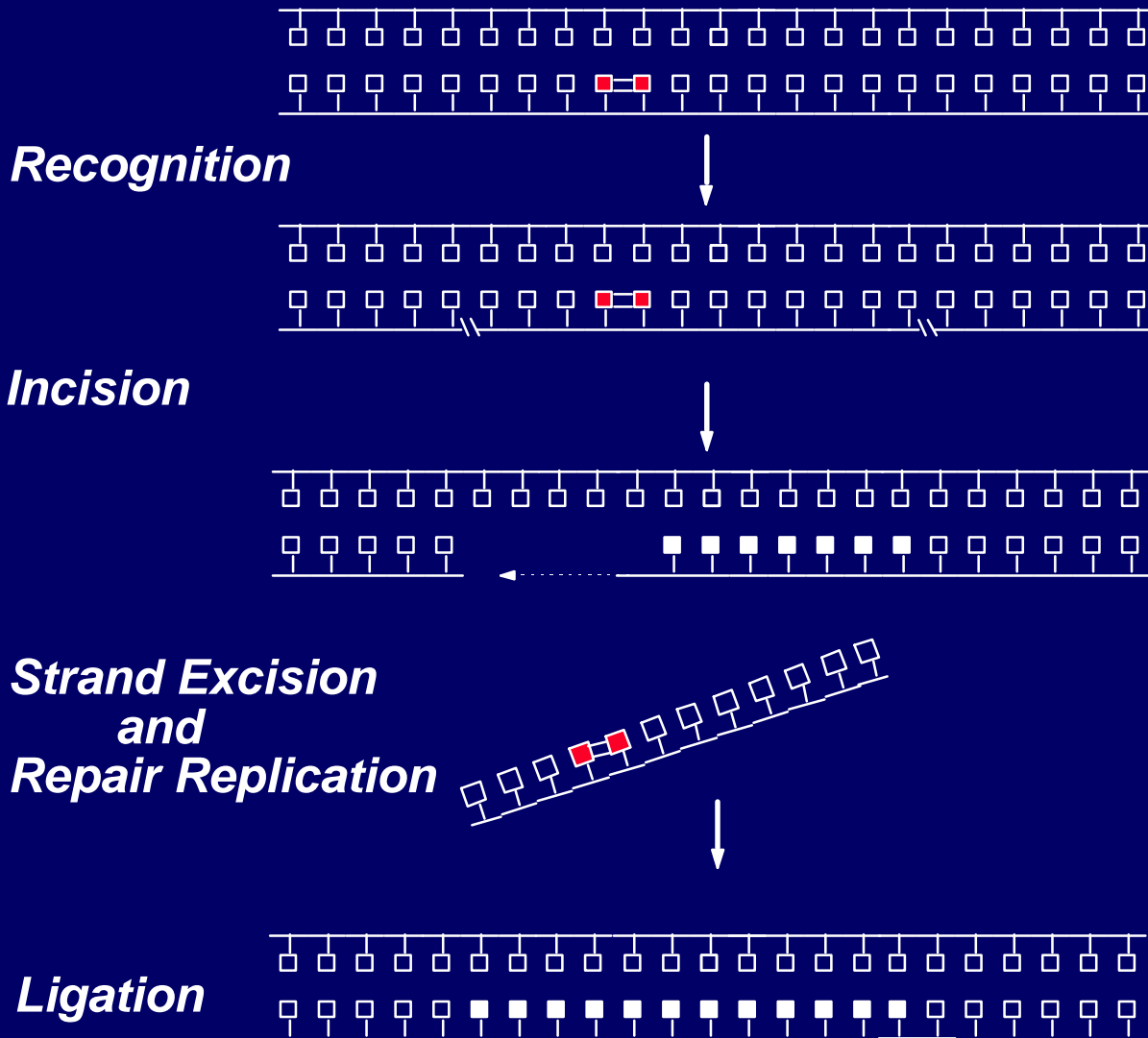
Types of Exogenous DNA Damage

- **Base Modification due to Reactive Oxygen Species**
Ionizing radiation, chemicals, UV-A
- **Alkylation and Interstrand cross links**
- **UV photodamage** - pyrimidine dimers
- **DNA-protein and carcinogen adducts**
- **Single and double-stranded DNA breaks**

Types of DNA Repair

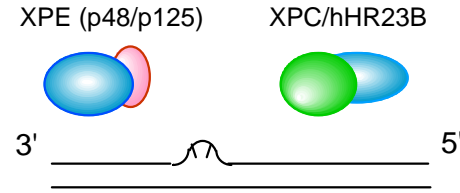
- **Excision Repair**
 - Nucleotide Excision Repair (NER)**
 - Base Excision Repair (BER)**
 - Mismatch Repair (MMR)**
- **Double-Strand Break Repair**
 - Homologous Recombination**
 - Non-Homologous End Joining**
- **Tolerance - Translesional DNA synthesis**

Nucleotide Excision Repair

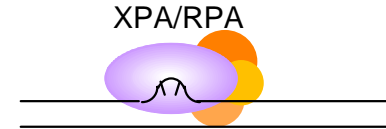


Human Nucleotide Excision Repair

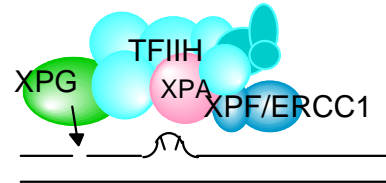
STRUCTURE DISTORTION



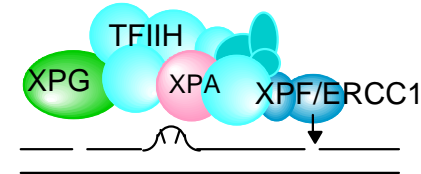
I. RECOGNITION



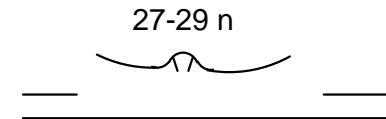
TFIIH [XPB and XPD helicases
p62, p52 p44, p34
CAK (Cdk7, cyclin H, Mat1)



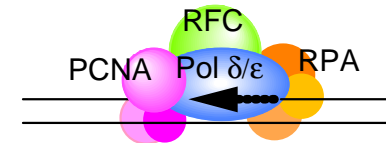
II. INCISION



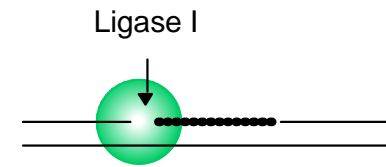
III. EXCISION



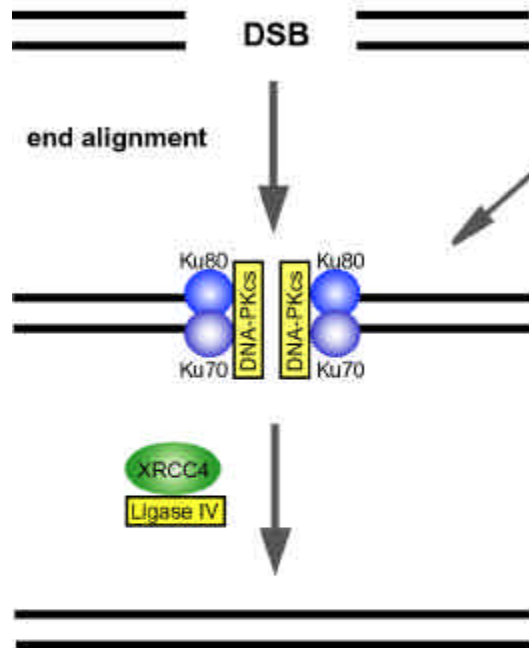
IV. REPAIR REPLICATION



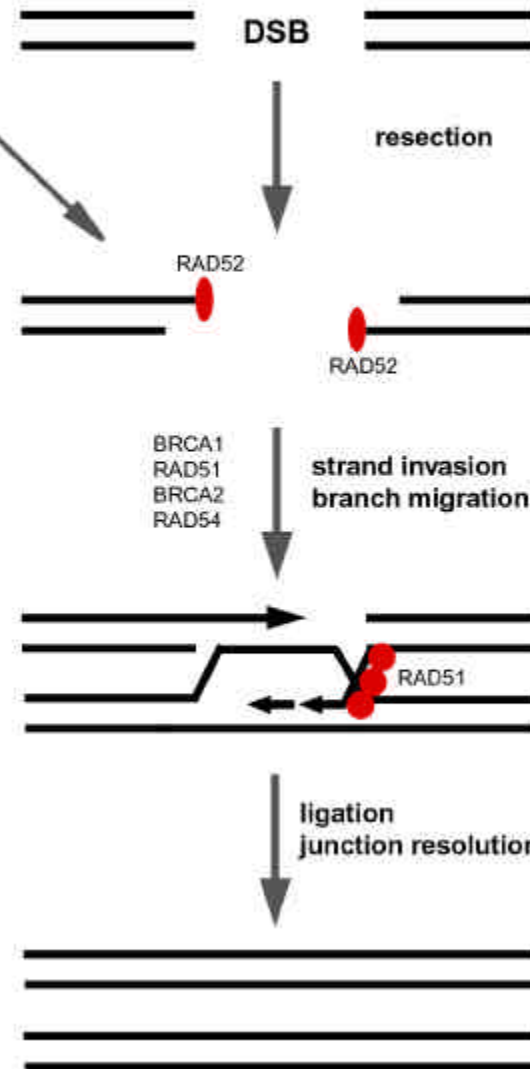
V. REJOINING



Non-Homologous End-Joining



Homologous Recombination



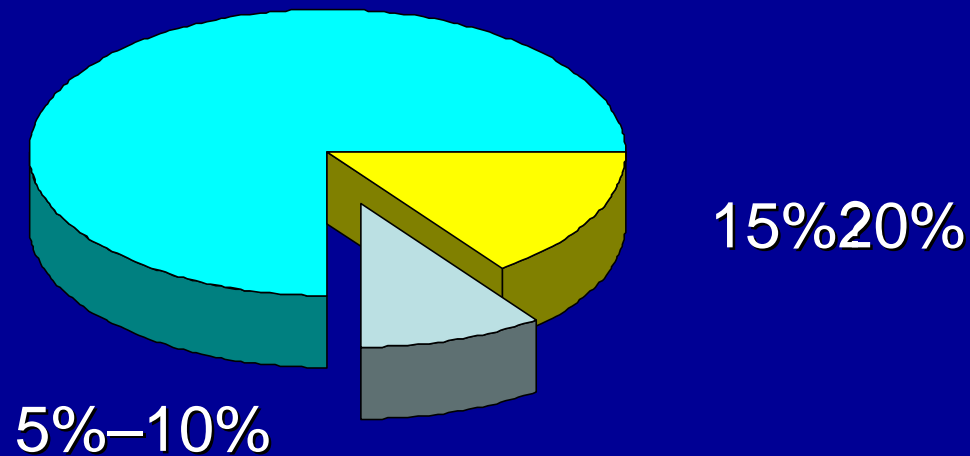
Evidence for DNA Damage Influencing Breast Cancer Risk

- Increased breast cancer incidence following exposure to DNA damage
 - X-irradiation treatment for Hodgkins lymphoma
 - Carcinogen exposure - oxidative radicals, estrogen
- Many gene found mutated in sporadic breast cancer or causing inherited breast cancer syndromes are involved in DNA repair pathways
 - p53, BRCA1, BRCA2, ATM, Fanconi's Anemia
- Polymorphisms in DNA repair genes are associated with increased risk
 - XRCC1, XPD, OGG1

DNA Repair in Breast Cancer

- **Risk Assessment**
 - Mutations or polymorphisms in DNA repair genes
 - Altered expression of DNA repair genes
 - DNA repair activity in pre-malignant tissues
- **Prevention**
 - Decreased DNA damage
 - Enhanced DNA repair
- **Treatment**
 - Targeted therapies to DNA repair defect in cancers

Incidence of Hereditary Breast Cancer



Breast Cancer

- Sporadic
- Family clusters
- Hereditary

Causes of Hereditary Susceptibility to Breast Cancer

Gene	Contribution
BRCA1	20-30%
BRCA2	10-30%
TP53	<1%
PTEN	<1%
STK11	<1%
ATM	?
Undiscovered genes	30-70%

BRCA1 Proposed Functions

Ubiquitin Ligase

Cell Cycle Regulation
G2/M and S

DNA Repair

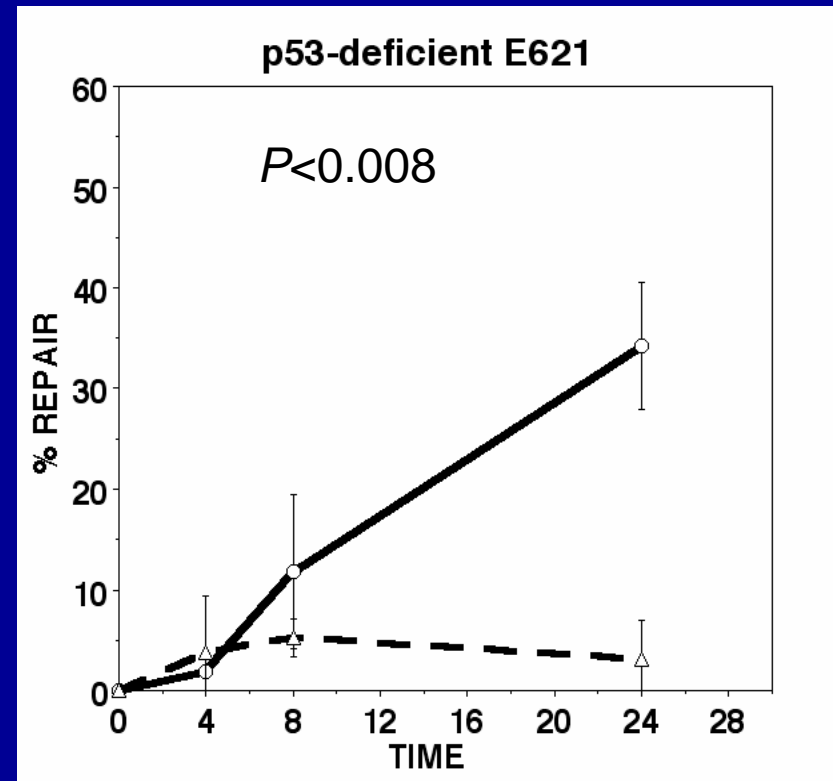
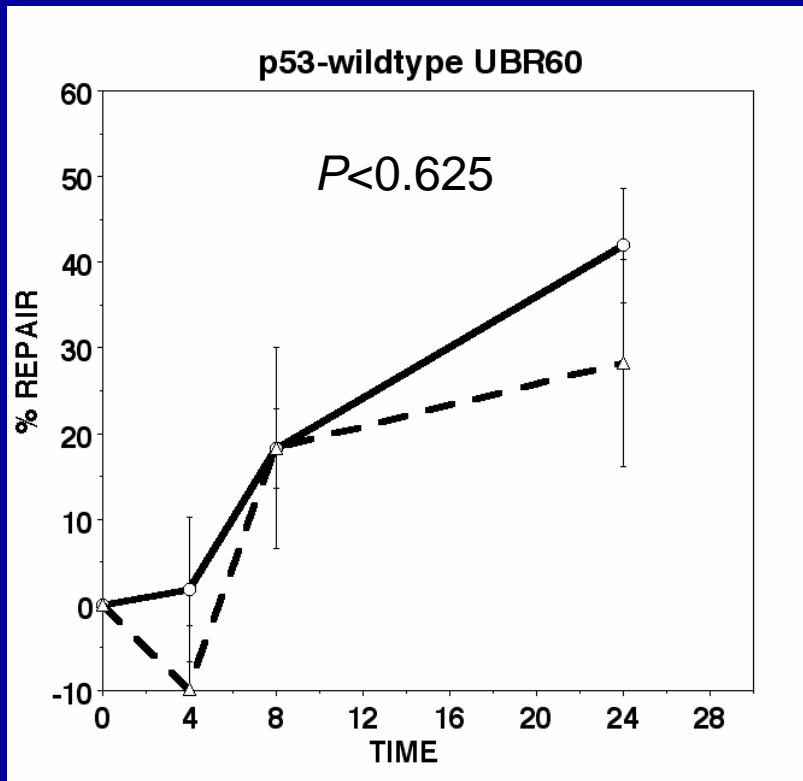
Homologous Recombination
Nucleotide Excision Repair

BRCA1

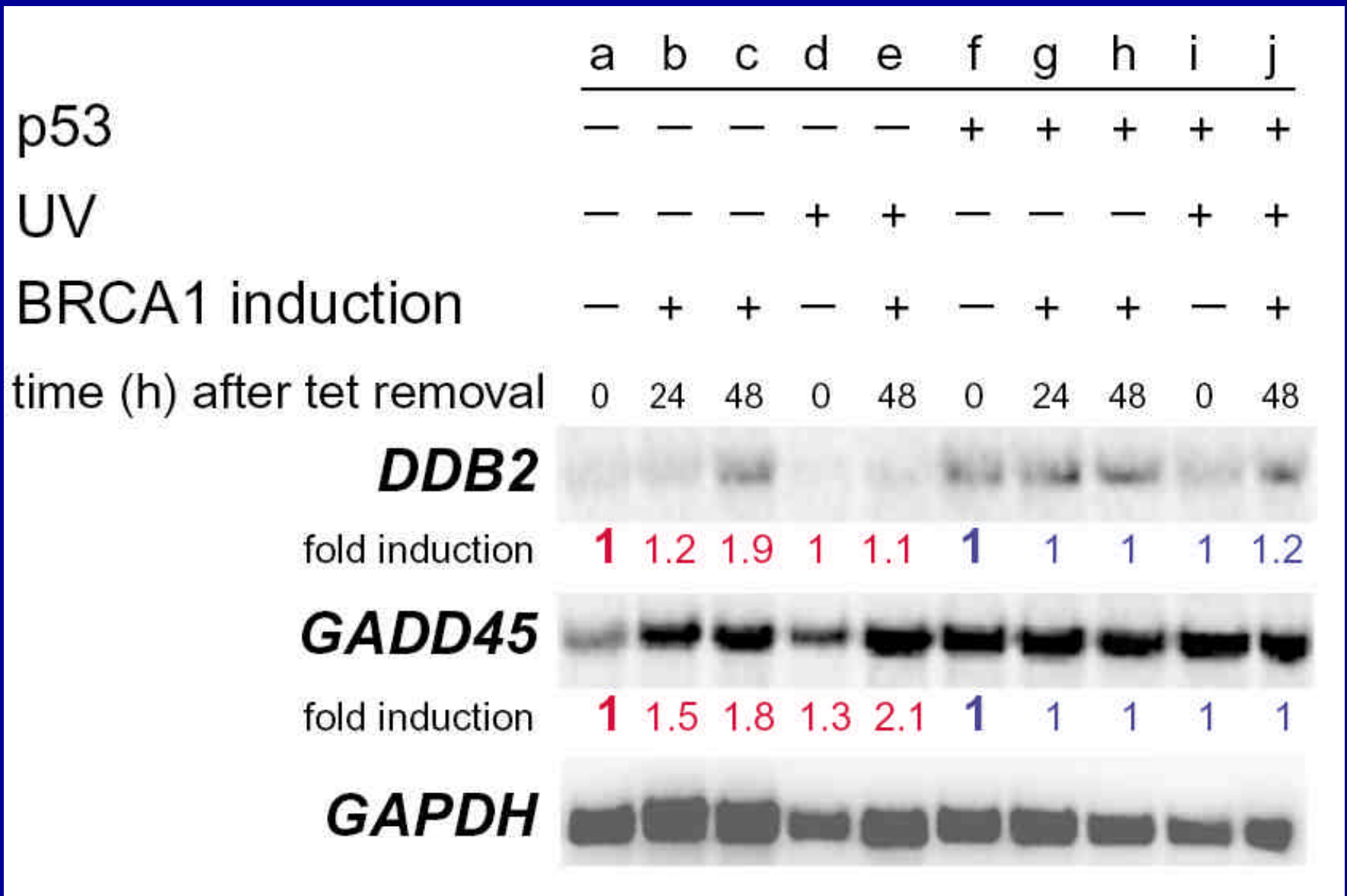
Mechanism?

- Transcription factor
- Chromatin remodeling
- protein/protein interactions

BRCA1 enhances GGR of CPDs in p53-deficient cells

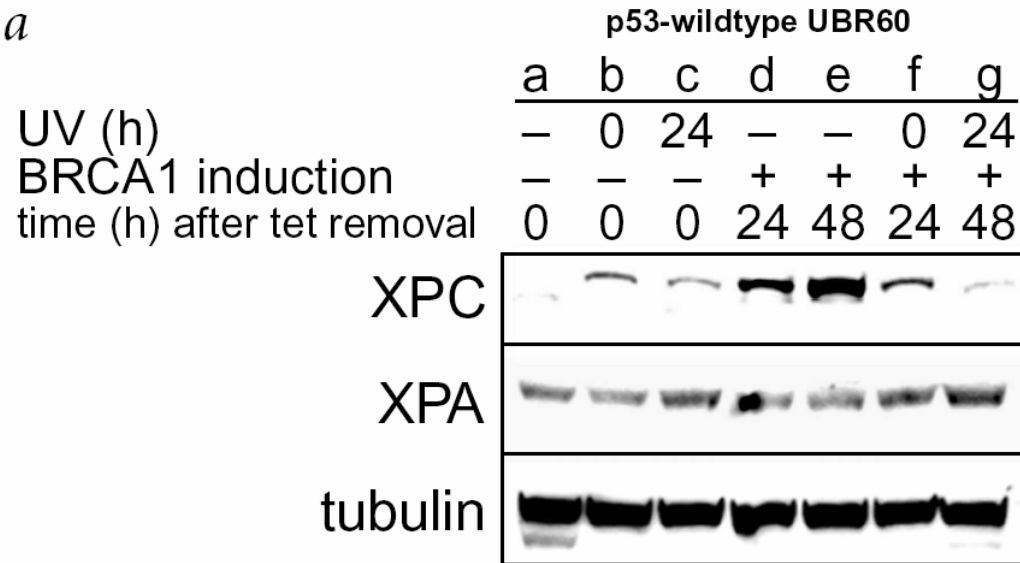


Activation of GADD45 and p48 by BRCA1

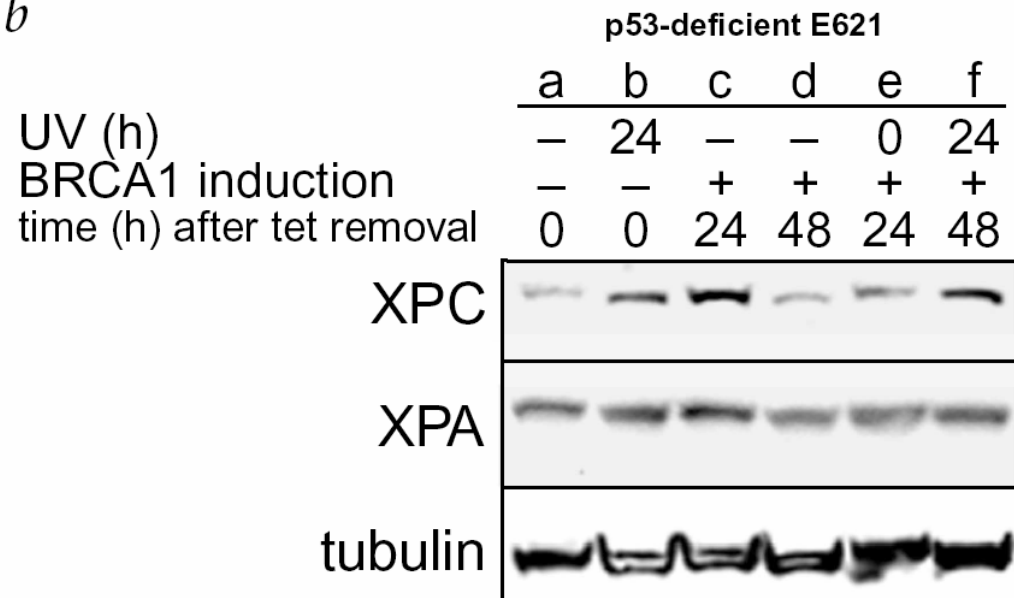


Activation of XPC, but not XPA by BRCA1

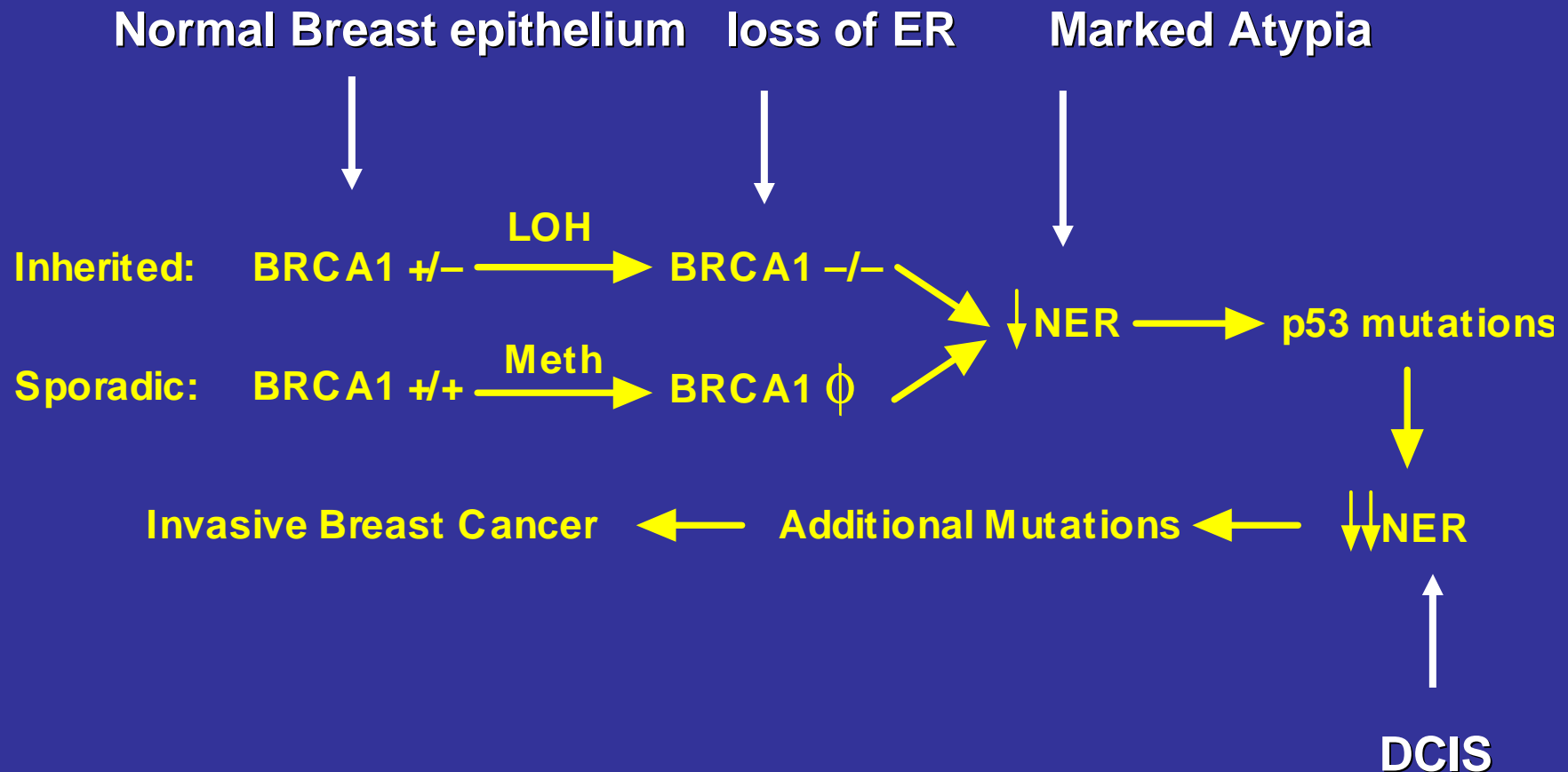
a



b



Model for BRCA1-associated Carcinogenesis



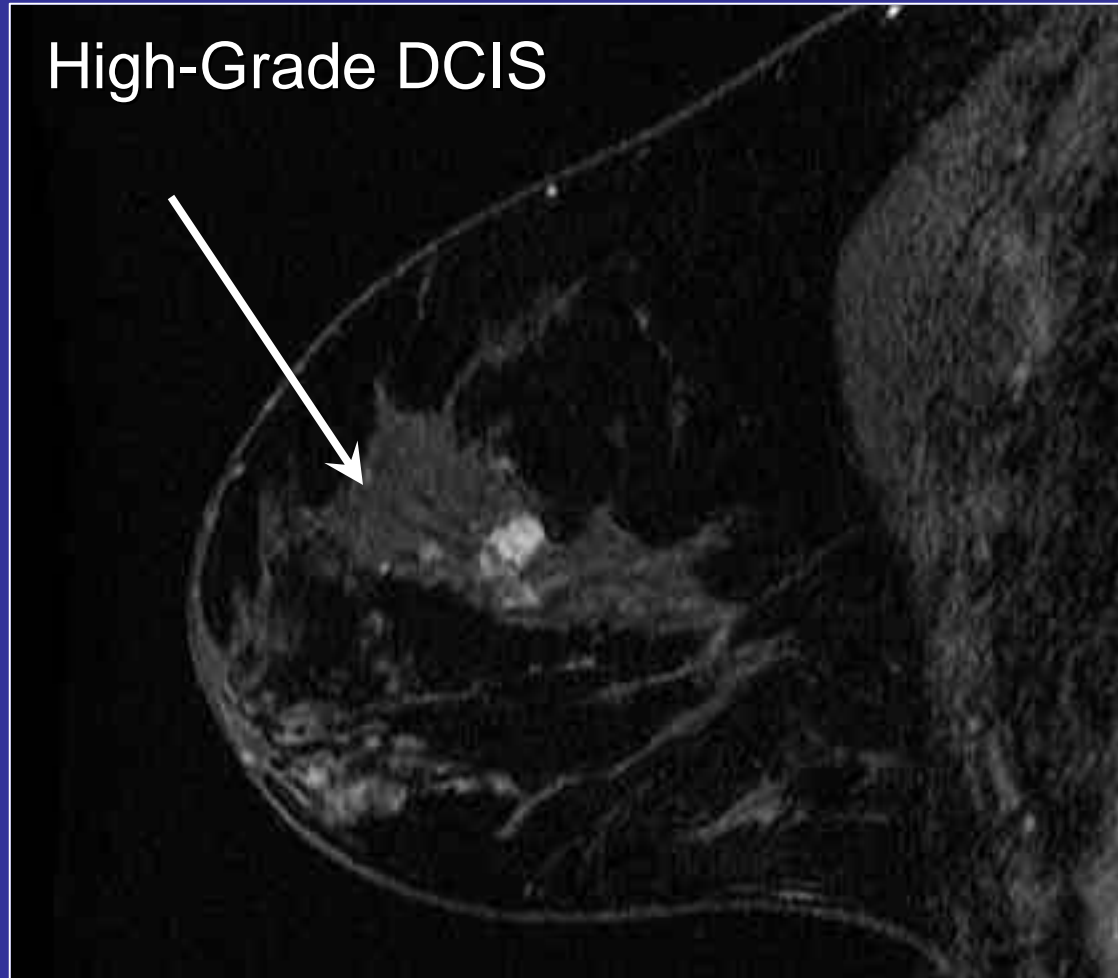
Comprehensive Breast Screening Protocol at Stanford

- Known Mutation carriers or Women with a 5-10 year risk of developing breast cancer 15% based on the Claus Model
- CBE, Mammography, MRI, and Ductal Lavage annually

Breast MRI Screening

- 4 published screening trials; 773 high-risk women
Sensitivity-72-100%; Specificity-25-60%
- Stanford MRI protocol produces high resolution images of lesion morphology and enhancement kinetics

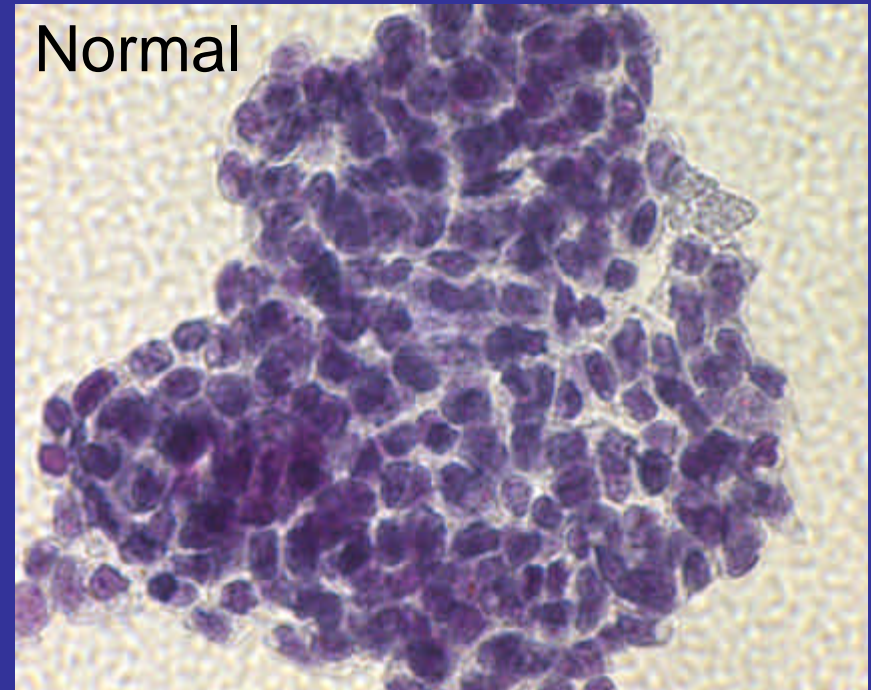
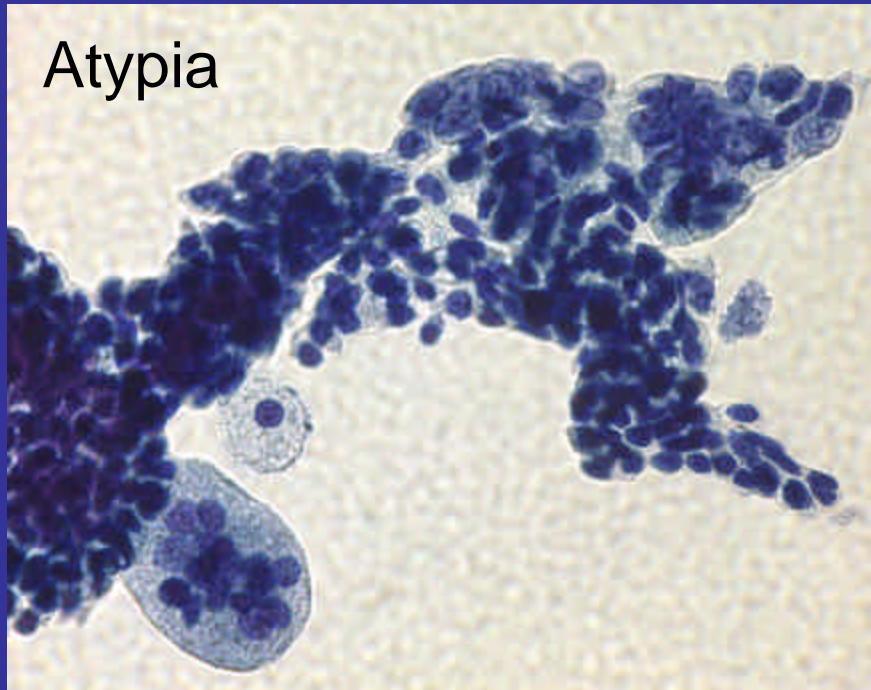
Screening MRI in High-Risk Women



Ductal Lavage

- Minimally invasive method of collecting breast ductal cells
- Can identify ADH and pre-malignant lesions
- Not intended for breast cancer detection

Ductal Atypia



Stanford Comprehensive Screening Experience

	Pts. seen	Pts. tested	+ test	Pts. screened	Pts. having PM
#	125	72	39	40	8
%		72% of pts. seen	54% of pts. tested	55% of pts. tested	11% of pts. tested

Screening MRI Biopsy Results

Invasive Cancer	0
DCIS	1
High-Risk Lesions	3
Benign Findings	7
PPV for Cancer	9%
PPV for High-Risk Lesions	27%

Ductal Lavage Screen Results

N=30

%

ICMD	3	10
Benign	20	67
Atypical	7	23
Malignant	0	0

Comprehensive Screening Protocol and Translational Studies

- **Gene Expression using Microarrays and RT-PCR**
- **Whole Genome Amplification and High-Throughput DNA sequencing for polymorphisms in DNA repair genes**
- **Functional DNA repair assays on mammary epithelial cells**

Acknowledgements

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