- DSBs are a major cytotoxic lesion – even a single unrepaired DSB can be a lethal event
- There are two different mechanisms of repair:
  - **Non homologous end joining** = does not depend on sequence homology
  - **Homologous recombination** = least likely to result in errors

**Defects in DNA repair or replication**

- All are associated with a high frequency of chromosome and gene (base pair) mutations; most are also associated with a predisposition to cancer, particularly leukaemia
- **Xeroderma pigmentosum**
  - Caused by mutations in genes involved in nucleotide excision repair (XP - genes)
  - Associated with a >1000 fold increase of sunlight induced skin cancer and with other types of cancer such as melanoma
- **Ataxia telangiectasia**
  - Caused by gene that detects DNA damage
  - Increased risk of X-ray induced DNA damage
  - Associated with increased breast cancer in carriers
- **Fanconi anaemia**
  - Caused by a gene involved in DNA repair
  - Increased risk of X-Ray and sensitivity to sunlight
- **Bloom syndrome**
  - Caused by mutations in a DNA helicase gene
  - Increased risk of X Ray and sensitivity to sunlight
- **Cockayne syndrome**
  - Caused by a defect in transcription-linked DNA repair
  - Sensitivity to sunlight
- **Werner’s syndrome**
  - Caused by mutations in a DNA helicase gene
  - Premature ageing in patients
- **Mismatch repair (which removes nucleotides which have been incorrectly incorporated during DNA replication) is deficient in hereditary non-polyposis colon cancer (HNPCC)**
- **Double strand break repair is defective in some familial breast cancers (BRCA 1 and BRCA 2 mutations) and in ataxia telangiectasia (ATM mutations). Fortunately, BRCA defective cells are hypersensitive to the chemotherapeutic drug cisplatin than breast cancers that don’t have the BRCA mutation**

**PARP inhibition and tumour selective synthetic lethality**

- **PARP (poly ADP ribose polymerase)** is involved in the recognition of single stranded break repairs (base damage removal)
- If a cell is deficient in one type of DNA damage repair, it will rely on another for compensation = synthetic lethality
- In a cell with normal functioning BRCA1/BRCA2, if single stranded break repair is blocked by PARP, it will still be able to carry out other forms of DNA repair to make the cell survive eg. Homologous recombination.
- In abnormal cells with inhibition of single stranded break repair by PARP and dysfunctional BRCA1/2 means homologous recombination is also impaired.