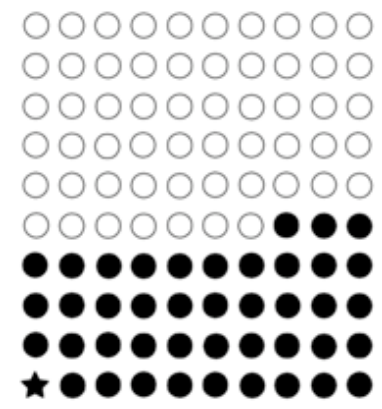
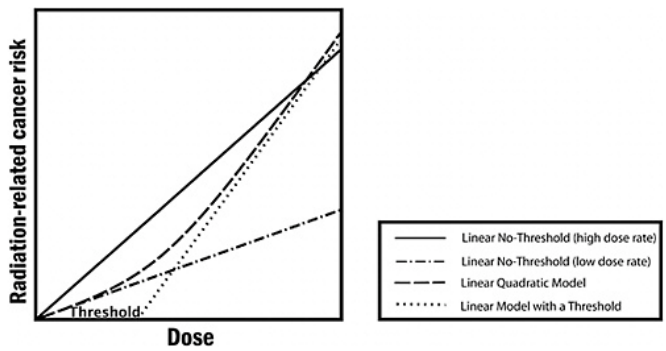
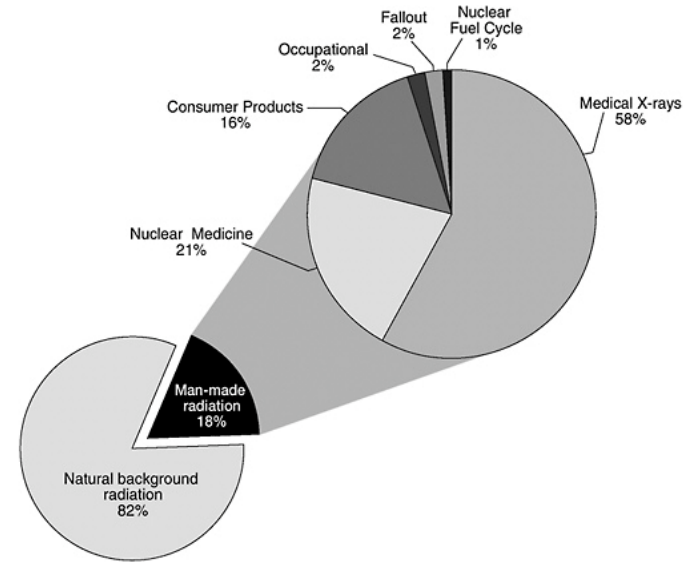
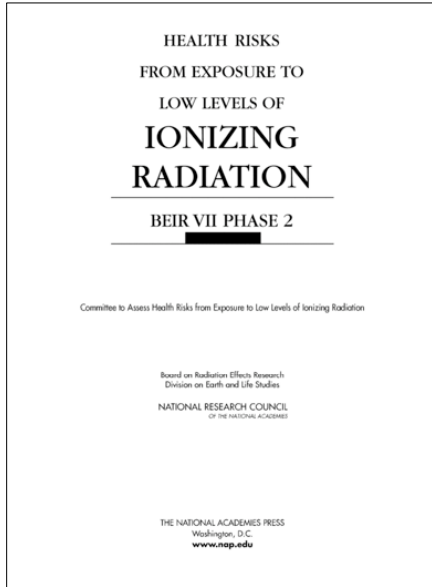
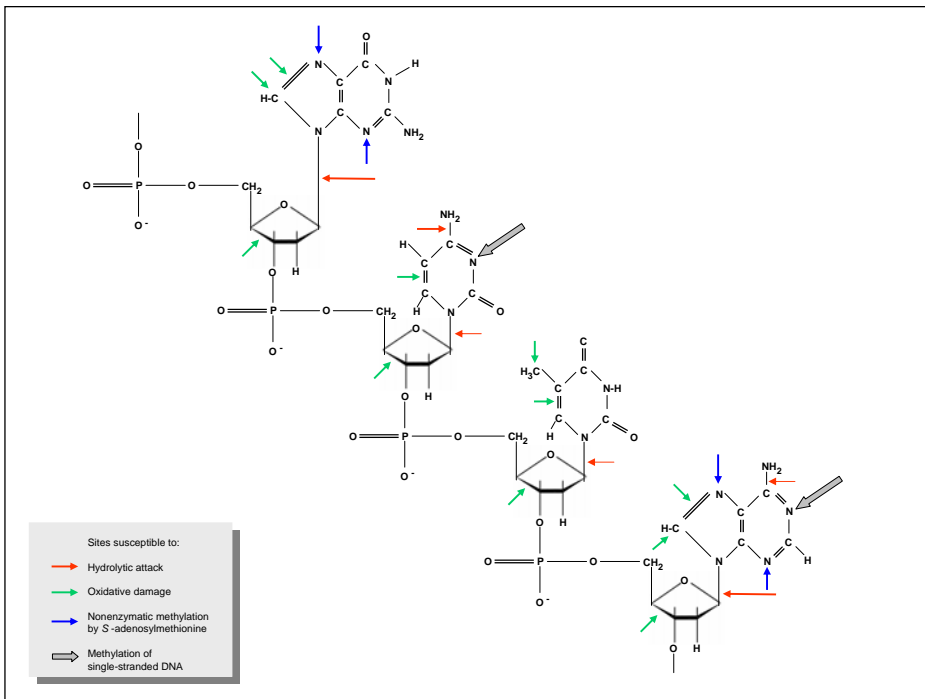


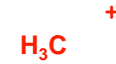
U.S. National Academy of Sciences, 2006  
 18 authors including T. Lindahl :



In a lifetime, approximately 42 (solid circles) of 100 people will be diagnosed with cancer. Calculations in this report suggest that approximately one cancer (star) per 100 people could result from a single exposure to 0.1 Sv of low-LET radiation above background.

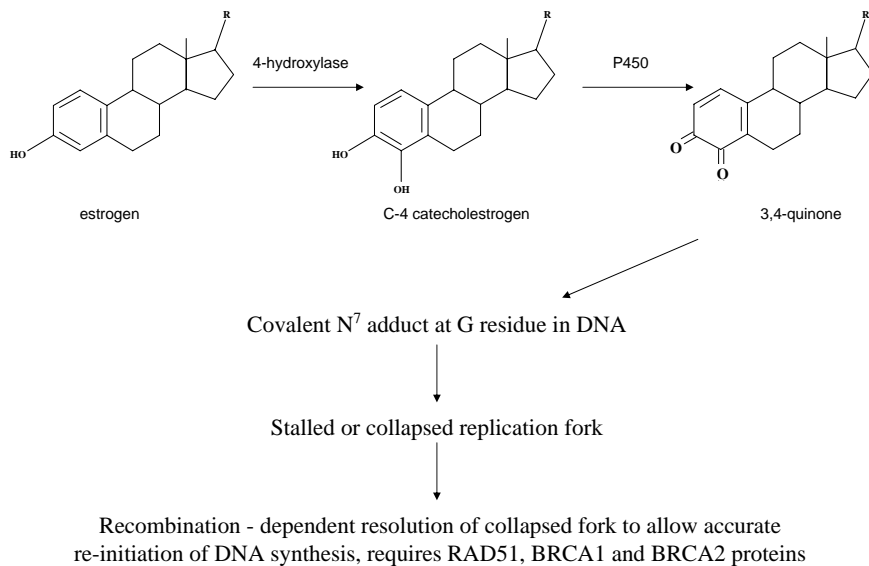


## S-adenosylmethionine



© 2007 TCI and S. 107-120 (10/2007) and are not to be used for other purposes.

### Model for tissue specificity by an endogenous carcinogen



### Estimated Spontaneous DNA Lesions in a Mammalian Cell (Numbers of Altered Nucleotide Residues in a 3×10<sup>9</sup> bp Genome after 24h at 37°C)

	100% double-stranded DNA	98% double-stranded DNA 2% single-stranded DNA
<b>Hydrolysis</b>		
Depurination	9000	9000
Depyrimidination	300	300
Cytosine deamination	50	250
5-Methylcytosine deamination	5	25
<b>Oxidation</b>		
8-Hydroxyguanine (8-oxoG)	500-1000	500-1000
Ring-saturated pyrimidines (thymine glycol, cytosine hydrates)	~1000	~1000
Lipid peroxidation products (M <sub>1</sub> G, etheno-A, etheno-C)	~1000	~1000
<b>Non-enzymatic methylation by S-adenosylmethionine</b>		
7-Methylguanine	3000	3000
3-Methyladenine	600	600
1-Methyladenine/3-methylcytosine	ND	100
<b>Non-enzymatic methylation by nitrosated polyamines and peptides</b>		
O <sup>6</sup> -Methylguanine	10-50	10-50

Lindahl and Barnes, CSHSQB, 2000.

## Endogenous DNA lesions as risk factors in human cancer

Supporting evidence:

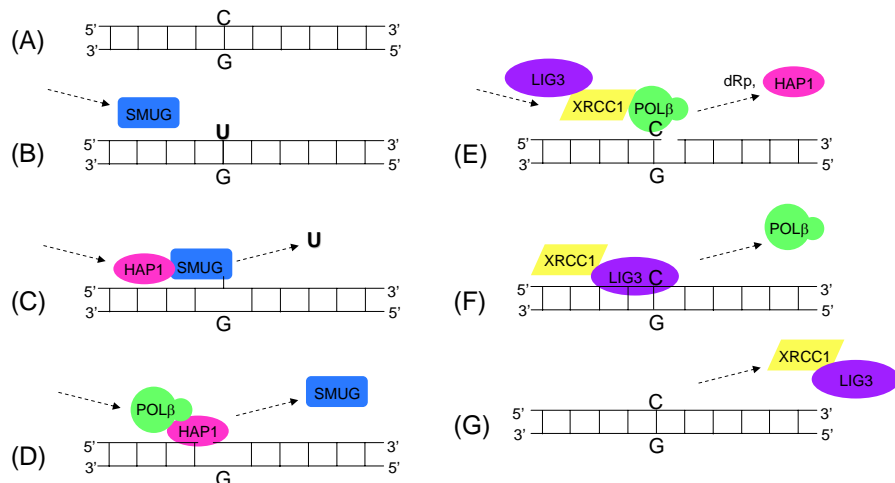
- Several pro-mutagenic mechanisms of endogenous DNA damage have been identified
- Defects in mammalian DNA repair enzymes acting on spontaneous DNA lesions have been associated with several forms of cancer
- Epidemiological research has not identified new major cancer-causing agents in our environment beyond ultraviolet light and cigarette smoke

## O<sub>2</sub>

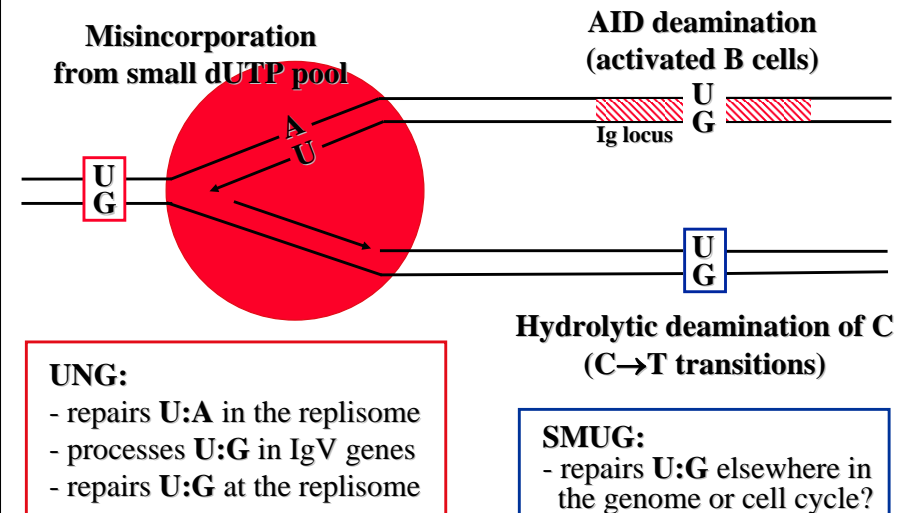
- Oxygen is a toxic and mutagenic gas.
- Life on Earth originated under essentially anaerobic conditions.
- A major environmental catastrophe occurred when the blue-green algae developed the ability of photosynthesis; tonnes of the by-product O<sub>2</sub> were released into the atmosphere and most early forms of life were killed by this air pollutant.
- Subsequently, many surviving organisms evolved the use of O<sub>2</sub>-based energy production (mitochondria) and developed antioxidant defense mechanisms.

(Halliwell & Gutteridge, Free Radicals in Biology and Medicine, 3rd ed.,

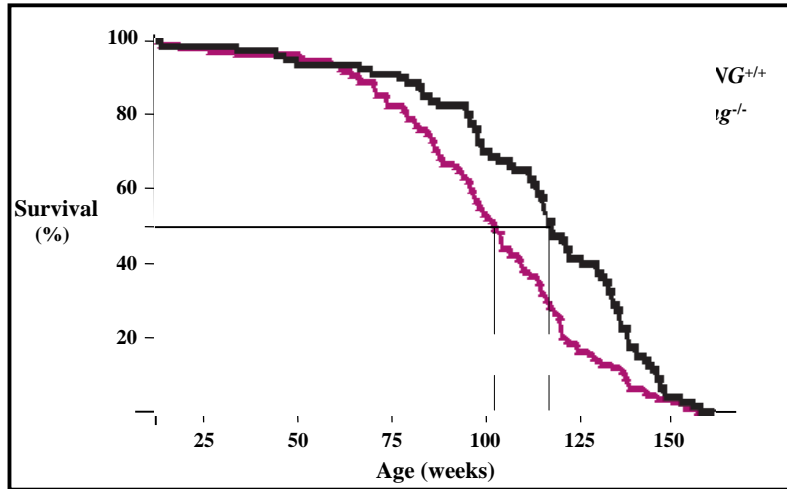
### BASE EXCISION REPAIR IN HUMAN CELLS (of deaminated cytosine by the SMUG DNA glycosylase)



## Incidence and consequences of uracil in the mammalian genome

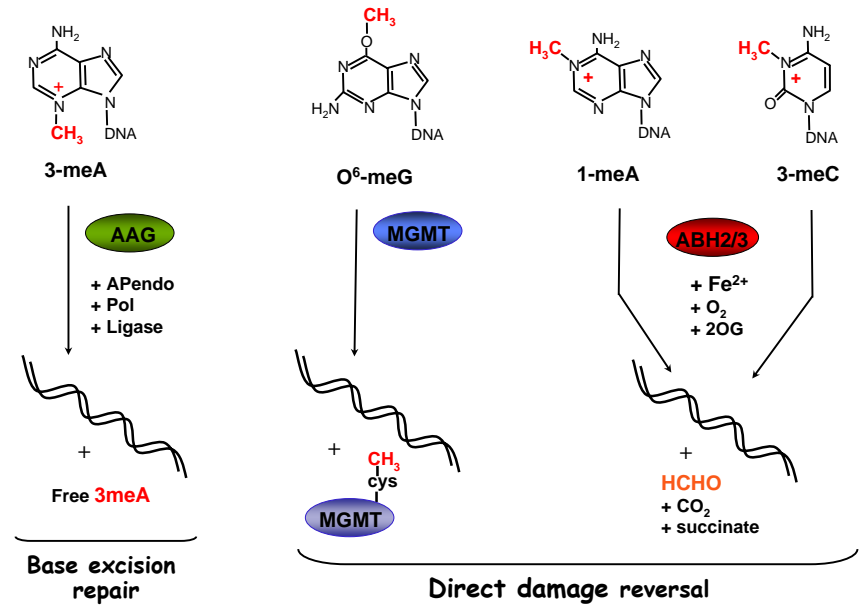


## Increased morbidity of UNG-deficient mice



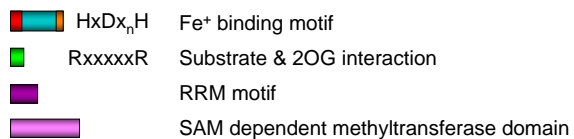
~100 mice of each genotype were monitored

## Three mechanisms of repair of methylated DNA bases

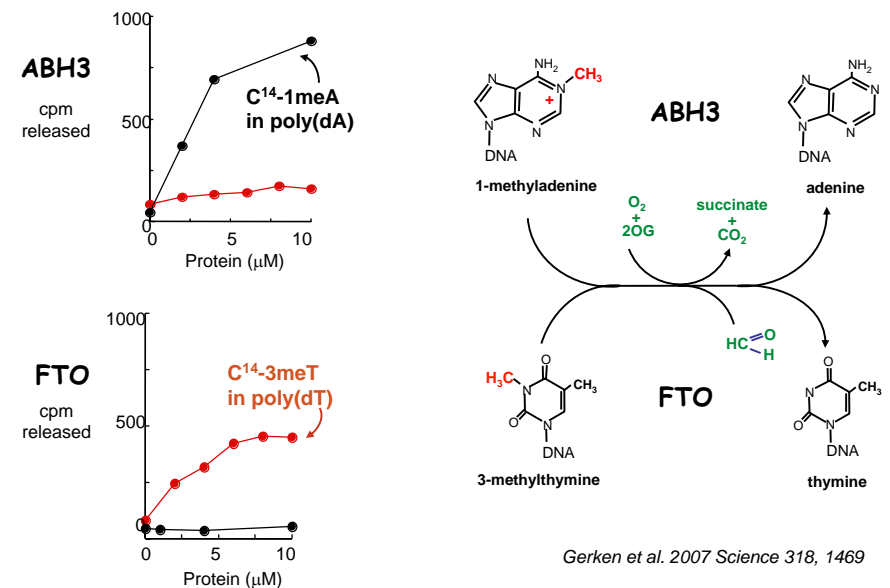


## Human homologues of *E. coli* AlkB

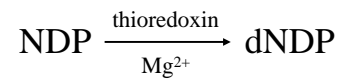
<i>E. coli</i> AlkB	aa's	locus
hABH1	216	14q24
hABH2	389	12q23
hABH3	261	11p11
hABH4	286	7q22
hABH5	302	17p11
hABH6	394	19q13
hABH7	265	19p13
hABH8	221	11q23
FTO	664	16q12
FTO	505	16q12



## Demethylation of 3-methylthymine in DNA by FTO



# Ribonucleotide reductase



An unusual enzyme of two different subunits with an iron centre, oxygen bridge and a stable tyrosine-derived free radical at the active site.  
Sensitive to quenching of the free radical by hydroxyurea.