Chemical Carcinogenesis
November 17 2016

Cancer Incidence and Death rates by Geography

Countries showing highest and lowest incidence of specific types of cancer[a]			
Cancer site	**Country of highest risk**	**Country of lowest risk**	**Relative risk H/L[b]**
Skin (melanoma)	Australia (Queensland)	Japan	155
Lip	Canada (Newfoundland)	Japan	151
Nasopharynx	Hong Kong	United Kingdom	100
Prostate	U.S. (African American)	China	70
Liver	China (Shanghai)	Canada (Nova Scotia)	49
Penis	Brazil	Israel (Ashkenazic)	42
Cervix (uterus)	Brazil	Israel (non-Jews)	28
Stomach	Japan	Kuwait	22
Lung	U.S. (Louisiana, African American)	India (Madras)	19
Pancreas	U.S. (Los Angeles, Korean American)	India	11
Ovary	New Zealand (Polynesian)	Kuwait	8
Geographic areas showing highest and lowest death rates from specific types of cancer[c]			
Cancer site	**Area of highest risk**	**Area of lowest risk**	**Relative risk H/L[b]**
Lung, male	Eastern Europe	West Africa	33
Esophagus	Southern Africa	West Africa	16
Colon, male	Australia, New Zealand	Middle Africa	15
Breast, female	Northern Europe	China	6

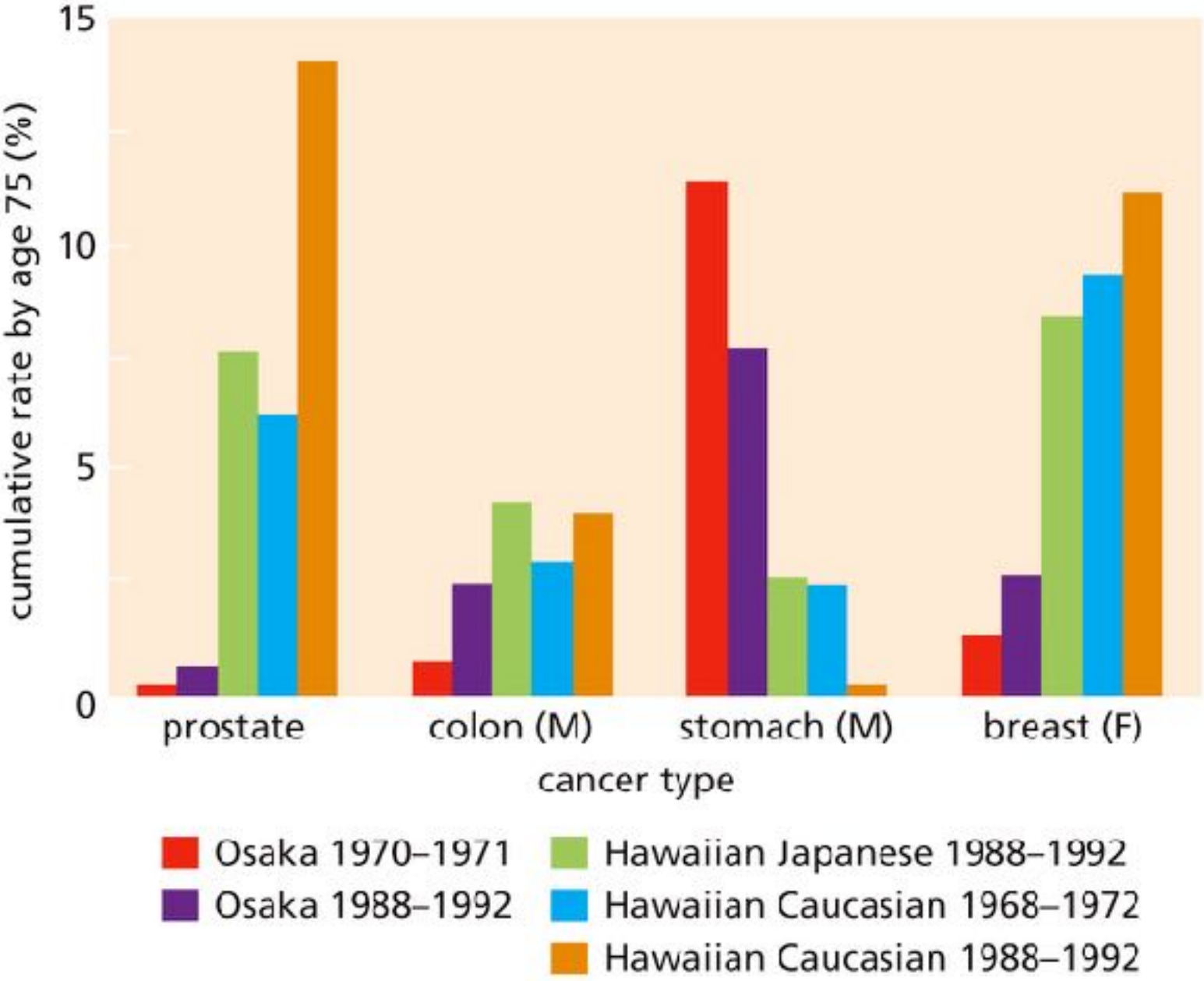


Figure 2.23 The Biology of Cancer (© Garland Science 2014)

Epidemiological studies of cancer incidence indicate:

1. The incidence rates for specific organ tumors varies among countries.

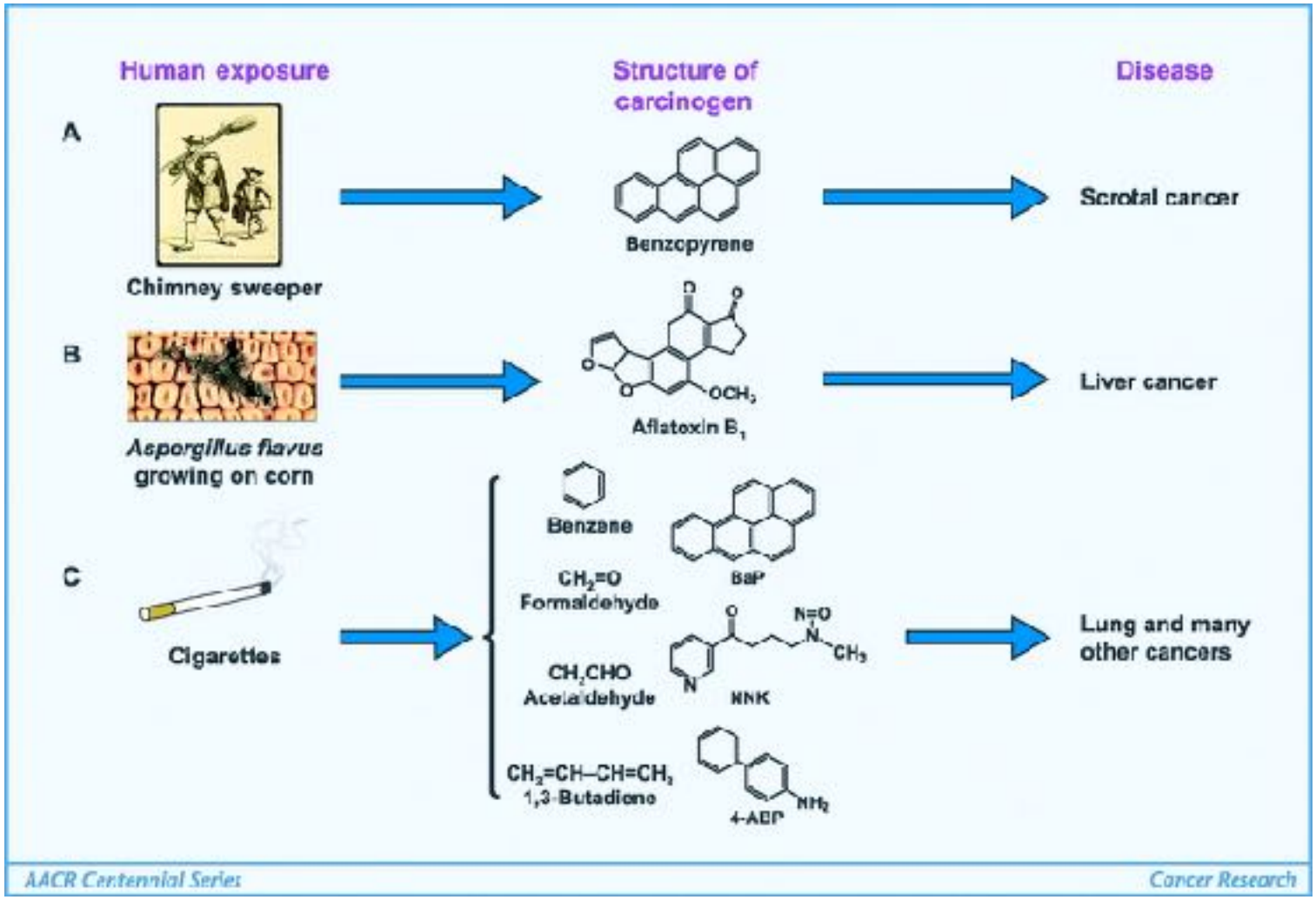
2. Migrant populations and their descendents acquire the pattern of cancer risk of the new country.

3. Over 80% of cancer deaths in Western industrial countries can be attributed to lifestyle factors such as diet (35%), tobacco (30%), alcohol (3.6%), infections and occupational exposures.

History of Chemical Carcinogenesis

- In 1567 Paracelsus suggested that the “wasting disease of miners” might be attributed to exposure to realgar (arsenic sulfide).
- In 1761, John Hill noted that nasal cancer occurred in some people who used snuff excessively and in 1859 Bouisson described oral cancer in tobacco smokers.
- The London surgeon Percival Pott in reported in 1775 that cancer of the scrotum sometimes developed in men after being exposed in childhood when they worked as chimney sweeps.
- Epidemiological evidence has been important in detecting carcinogenic substances.
- Rehn (1895) reported an increased incidence of bladder cancer in aniline dye workers in Germany. The major carcinogen involved is now believed to be 2-naphthylamine.
- Work with radium suggested the induction of skin cancer by repeated X-ray burns and in 1910 to 1912, Marie, Clunet and Raulot-Lapointe reported the induction of sarcoma in rats by the application of X-irradiation.
- The first chemical induction of cancer in laboratory animals was achieved by Yamagiwa and Ichikawa (1915) by painting coal tar on the ears of rabbits every 2-3 days for more than a year.
- The first pure carcinogen, 1,2,5,6-dibenzanthracene, was synthesized in 1929 and in the 1930s Kenneway and Cook and their associates isolated carcinogenic polycyclic aromatic hydrocarbons including benzo(a)pyrene from coal tar.
- In the early 1900s, Boveri proposed a mutation theory of carcinogenesis but at that time it was not amenable to chemical investigation.

Exposure of humans to chemical agents and the identification of the cancer-causing molecular species.



Loeb L A , and Harris C C Cancer Res 2008;68:6863-6872

Cigarette consumption and lung cancer

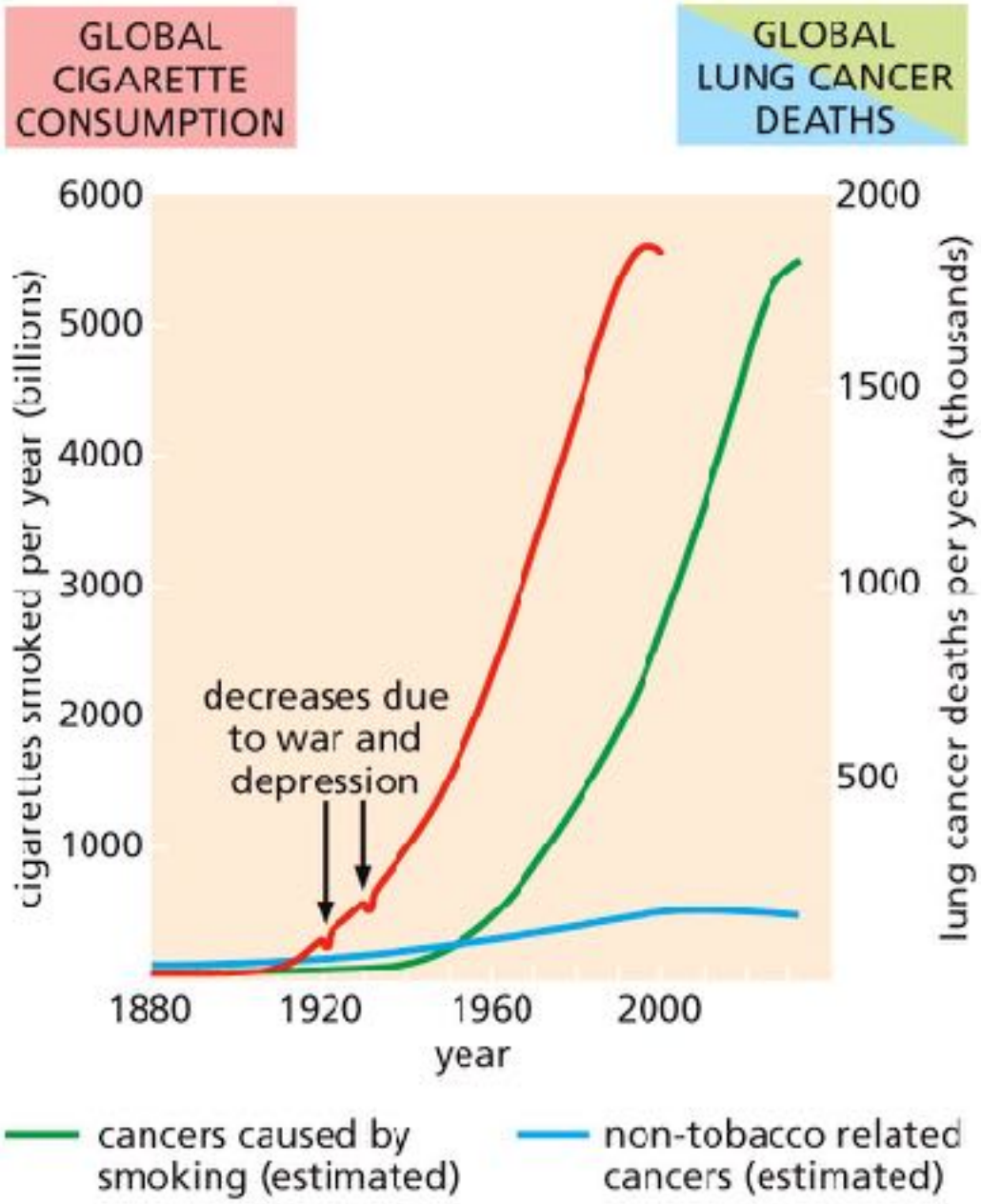


Figure 11.2 The Biology of Cancer (© Garland Science 2014)

MUTATION AND CARCINOGENESIS

Boveri was the first to suggest that chromosomal changes lead to cancer and in 1916 Tyzzer introduced the term “somatic mutation”. Evidence in favor of the somatic mutation theory has been summarized as follows:

1. Most chemical carcinogens are mutagens
2. Most carcinogens and mutagens are strong electrophilic reactants.
3. Ionizing or ultraviolet radiation and most chemical carcinogens cause lesions in DNA.
4. Defects in DNA repair capacity are associated with a high risk of cancer.
5. A high frequency of chromosomal aberration is correlated with an increased risk of malignancy.
6. Cell transformation by oncogenic viruses implies a change in the genetic information.
7. A malignant phenotype is inherited in the cell line.
8. Tumors are mostly monoclonal in origin.
9. Chromosomal changes found in tumors are frequently found to be nonrandom.

Table 2.7 Known or suspected causes of human cancers

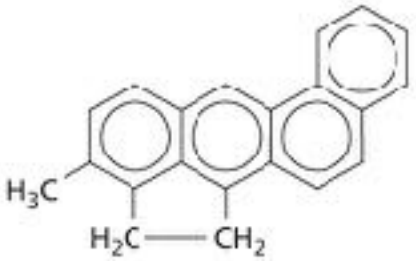
Specific carcinogenic agents implicated in the causation of certain cancers[c]	
Cancer	**Exposure**
Scrotal carcinomas	chimney smoke condensates
Liver angiosarcoma	vinyl chloride
Acute leukemias	benzene
Nasal adenocarcinoma	hardwood dust
Osteosarcoma	radium
Skin carcinoma	arsenic
Mesothelioma	asbestos
Vaginal carcinoma	diethylstilbestrol
Oral carcinoma	snuff
ER+ breast cancer[d]	hormone replacement therapy (E + P)[e]

[a]Adapted from American Cancer Society. Cancer Facts & Figures 1990. Atlanta: American Cancer Society, Inc.
[b]A large number of cancers are thought to be provoked by a diet high in calories (see Sidebar 9.10) acting in combination with many of these lifestyle factors.
[c]Adapted from S. Wilson, L. Jones, C. Coussens and K. Hanna, eds., Cancer and the Environment: Gene–Environment Interaction. Washington, DC: National Academy Press, 2002.
[d]ER+, estrogen receptor–positive.
[e]E + P, therapy containing both estrogen and progesterone.

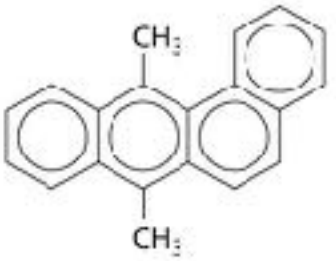
Structures of carcinogenic hydrocarbons

dibenz[*a*,*h*]anthracene

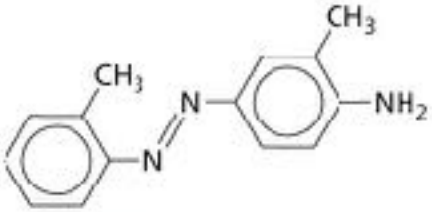
benzo[*a*]pyrene



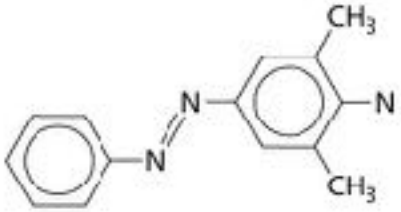
3-methylcholanthrene



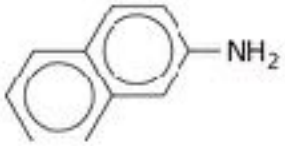
7,12-dimethylbenz[*a*]-arthracene



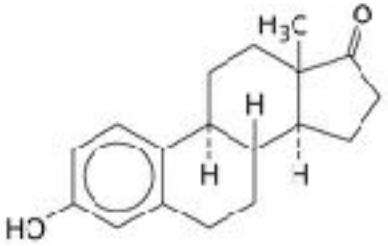
2′,3-dimethyl-4-amino-azobenzene



N,*N*-dimethyl-4-amino-azobenzene



2-naphthylamine



estrone

Figure 2.25 The Biology of Cancer (© Garland Science 2014)

TESTING IN LABORATORY ANIMALS

Testing in laboratory animals is the most reliable procedure for detecting carcinogenic activity. There can be metabolic and pharmacokinetic differences between species that make it preferable to examine more than one species.

Pure compounds should be administered to adequate numbers of test animals (not less than 10) and there should be appropriate controls.

The route of administration can influence the numbers of tumors and the tissues affected. The dose level must be high enough to see tumors in a statistically reliable number of animals. Chronic studies over the lifetime of the animal are necessary. Careful pathological examination of all dead animals is essential.

Diet, cage bedding and exposure to insecticides can all influence tumor induction.

Although pure compounds are essential for identification of a carcinogen such a test system will not detect the synergistic action of tumor initiators and promoters.

There is uncertainty on whether threshold levels exist for the detection of carcinogenic compounds.

IN VITRO TESTING OF CHEMICAL CARCINOGENS

- The high cost of animal screening has driven the search for short-term in vitro tests. The best known in vitro test is that devised by Bruce Ames which measure mutagenicity in a Salmonella strain that requires histidine for growth. Mutation can result in a reversion to the wild type phenotype that permits growth in the absence of histidine.
- Because many carcinogens require metabolic activation, the bacteria are incubated with a rat liver S9 fraction.
- The theoretical basis for tests of this type is the good but not perfect correlation between mutagenic and carcinogenic activity.
- For some studies this has been about 90% for large numbers of compounds but other studies have seen a correlation of about 75%.

The Ames test for measuring mutagenic capacity

Used to quantitatively assess the mutagenic potency of a test compound

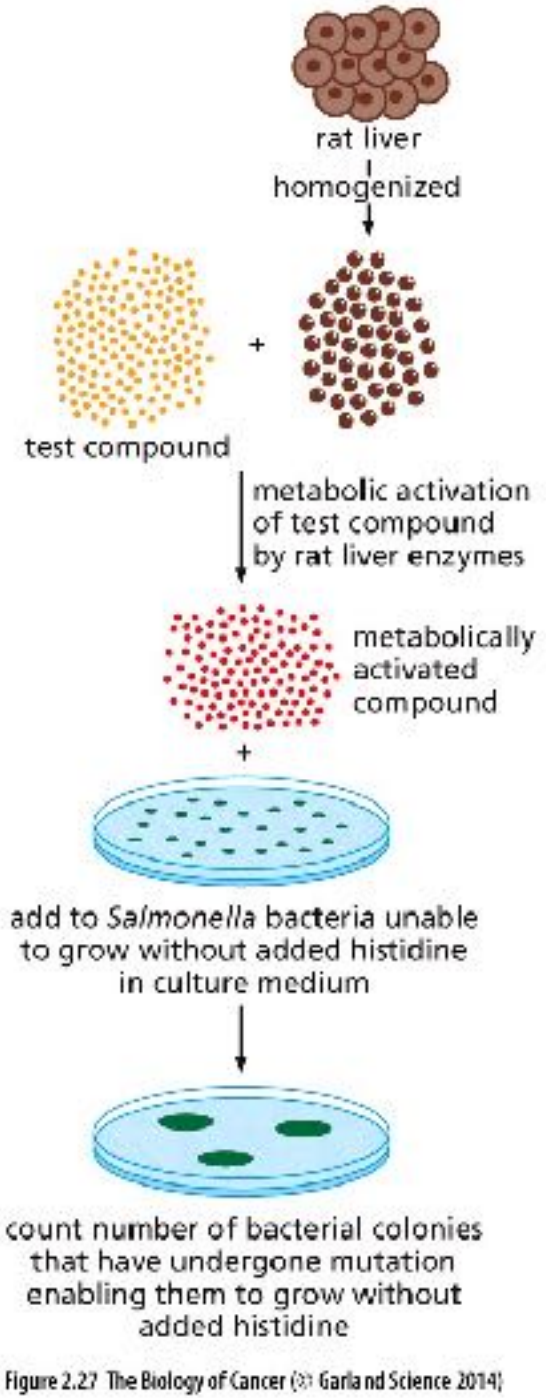


Figure 2.27 The Biology of Cancer (© Garland Science 2014)

Mutagenic versus Carcinogenic potency: most potent chemicals appear at the lower left

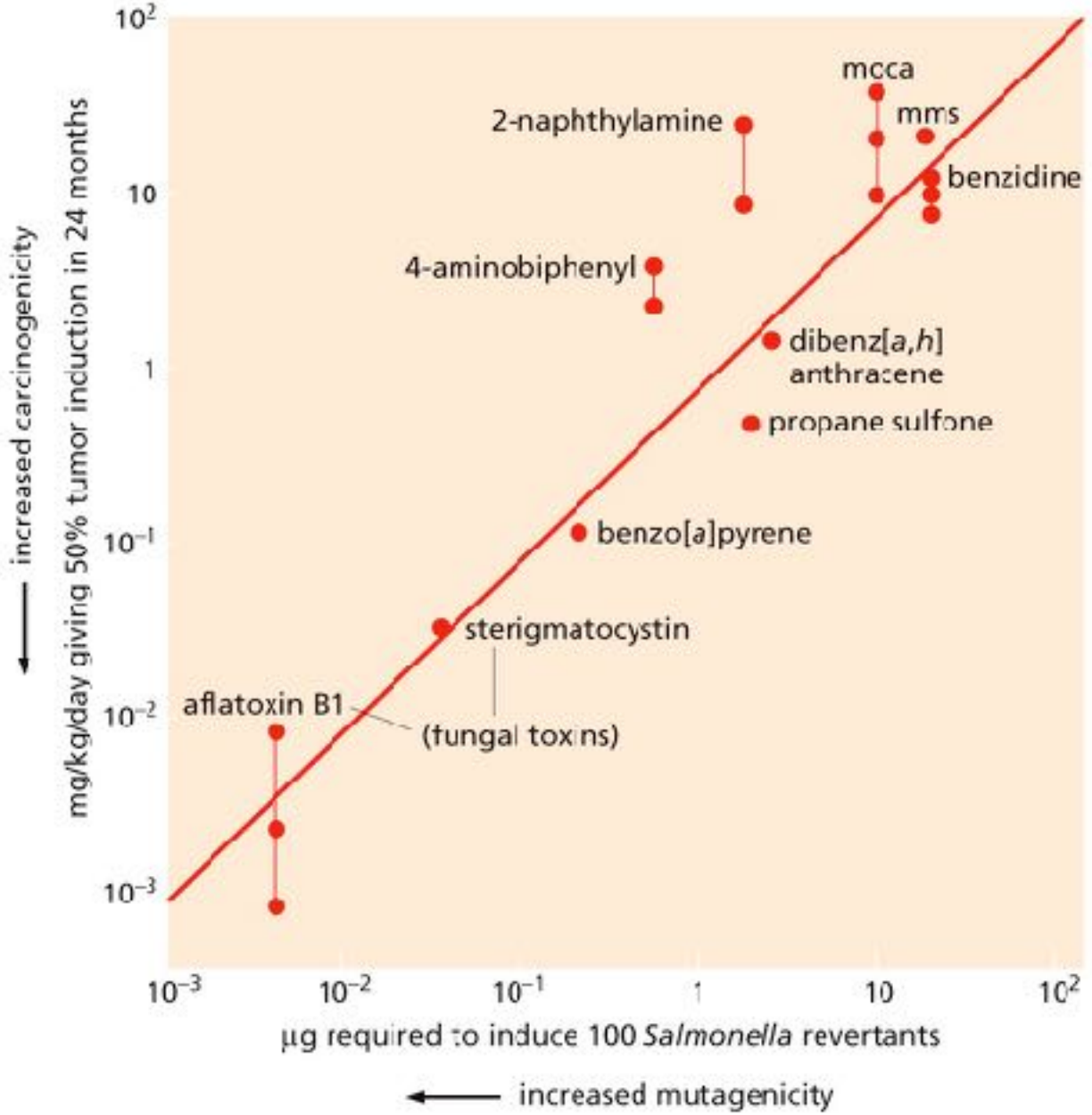
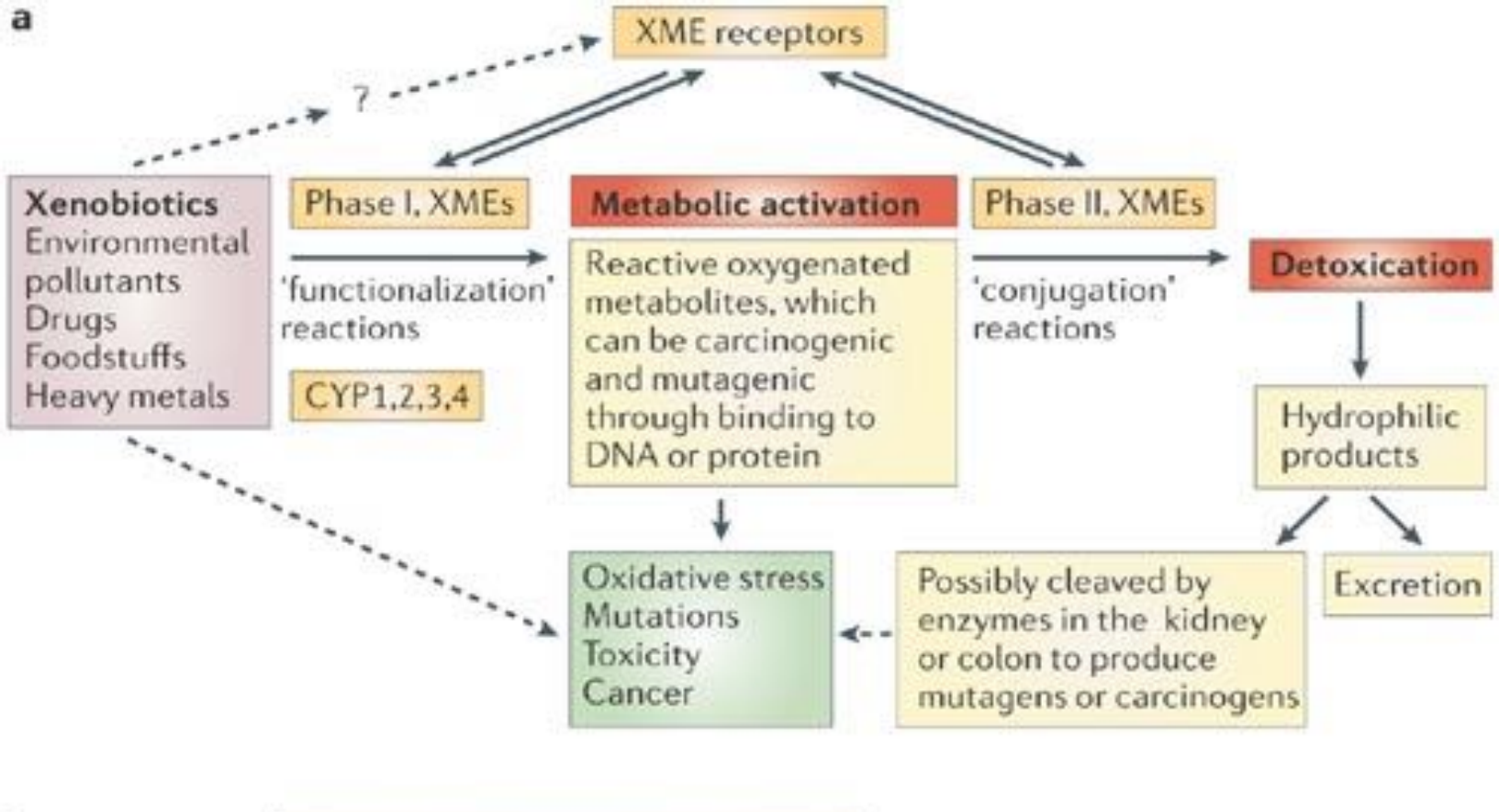


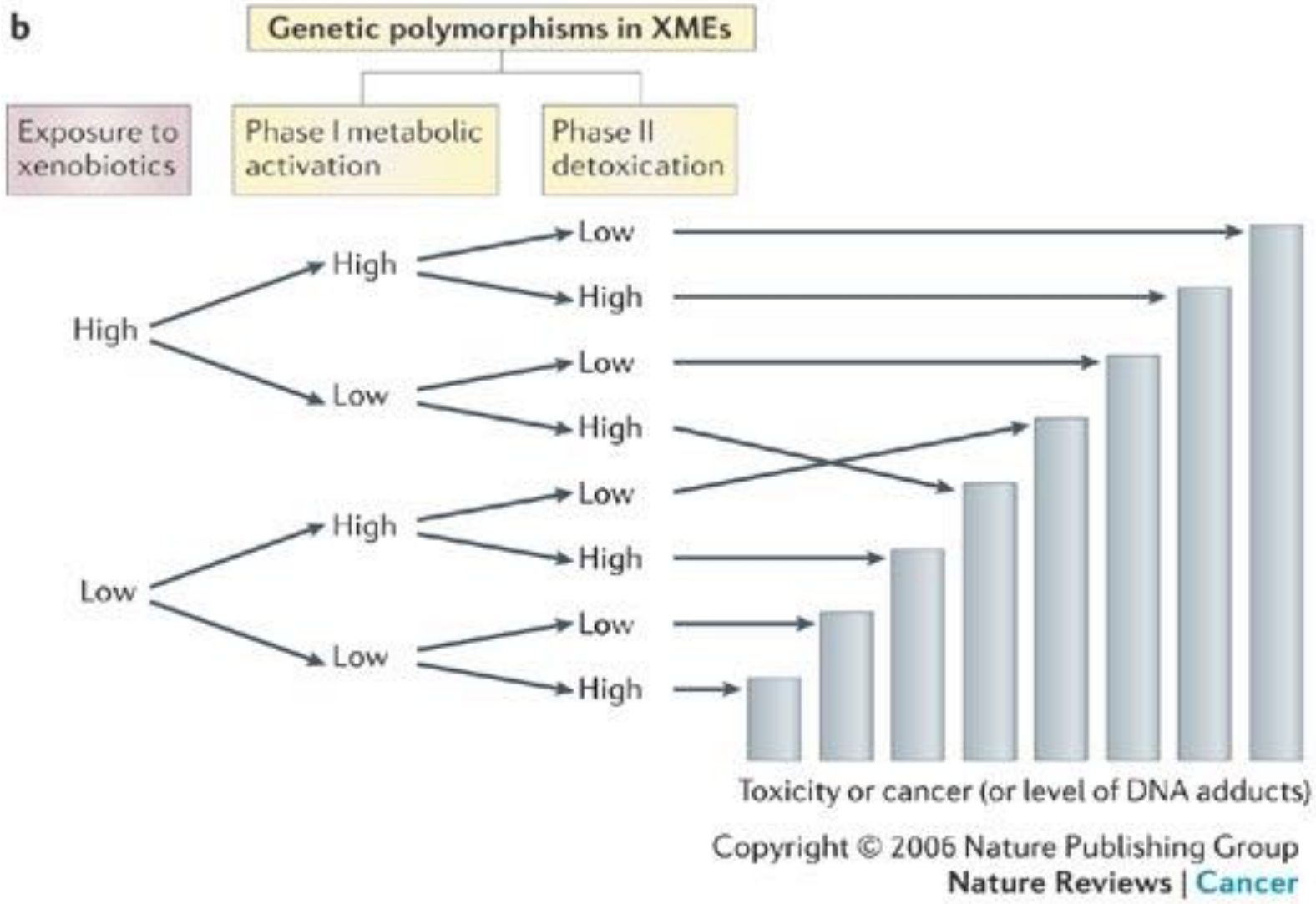
Figure 2.28 The Biology of Cancer (© Garland Science 2014)

Table 2.8 A sampling of Bruce Ames's roster of carcinogens identified in the normal diet[a]

Foodstuff	Compound	Concentration in foodstuff
Black pepper	piperine	100 mg/g
Common mushroom	agaritine	3 mg/g
Celery	furocoumarins, psoralens[b]	1 µg/g, 0.8 µg/g
Rhubarb	anthraquinones	varies
Cocoa powder	theobromine	20 mg/g
Mustard, horseradish	allyl isothiocyanate	varies
Alfalfa sprouts	canavanine[c]	15 mg/g
Burnt materials[d]	large number	varies
Coffee	caffeic acid	11.6 mg/g

Xenobiotic metabolizing Enzymes





Nature Reviews | Cancer

Actions of Cytochromes on Procarcinogens

Cytochrome P450s (CYPs) are involved in the biosynthesis of a variety of metabolites such as steroid hormones, cholesterol, and bile acids as well as degradation of fatty acids and steroids.

CYPs also aid in the oxidation and associated detoxification of xenobiotics such as drugs and carcinogens.

Among the xenobiotics entering the body are polycyclic aromatic hydrocarbons (PAHs) that derive from tobacco smoke, broiled foods and polluted environments.

Benzo[a]pyrene is a common PAH, which is converted to BPDE following reactions mediated by cytochrome P450 enzymes.

BPDE is a highly reactive molecule and can directly attack and form covalent adducts with DNA bases.

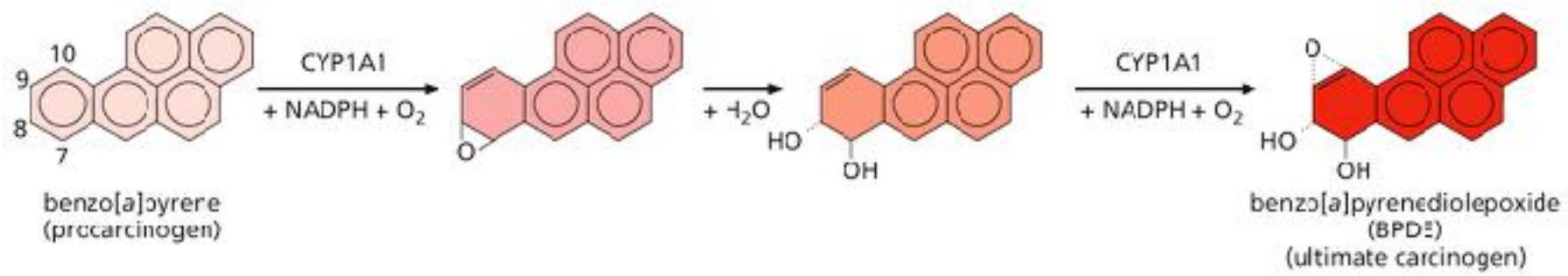


Figure 12.13b The Biology of Cancer (© Garland Science 2014)

DNA Adducts

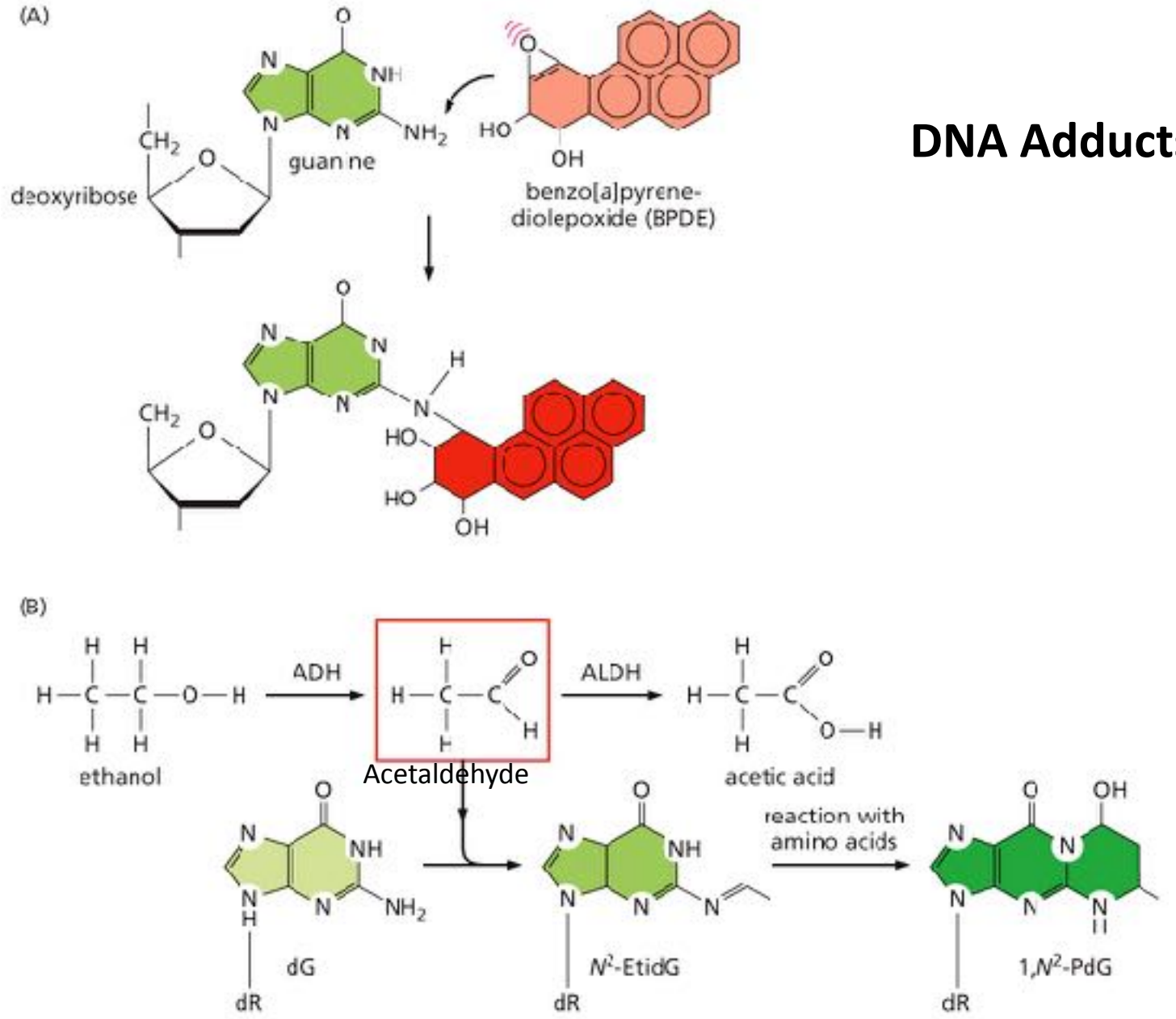


Figure 12.14 The Biology of Cancer (© Garland Science 2014)

Aflatoxin B1 and Liver carcinogenesis

Fungal toxin made by molds growing on improperly stored peanuts and grains.

One of the most potent mutagen known.

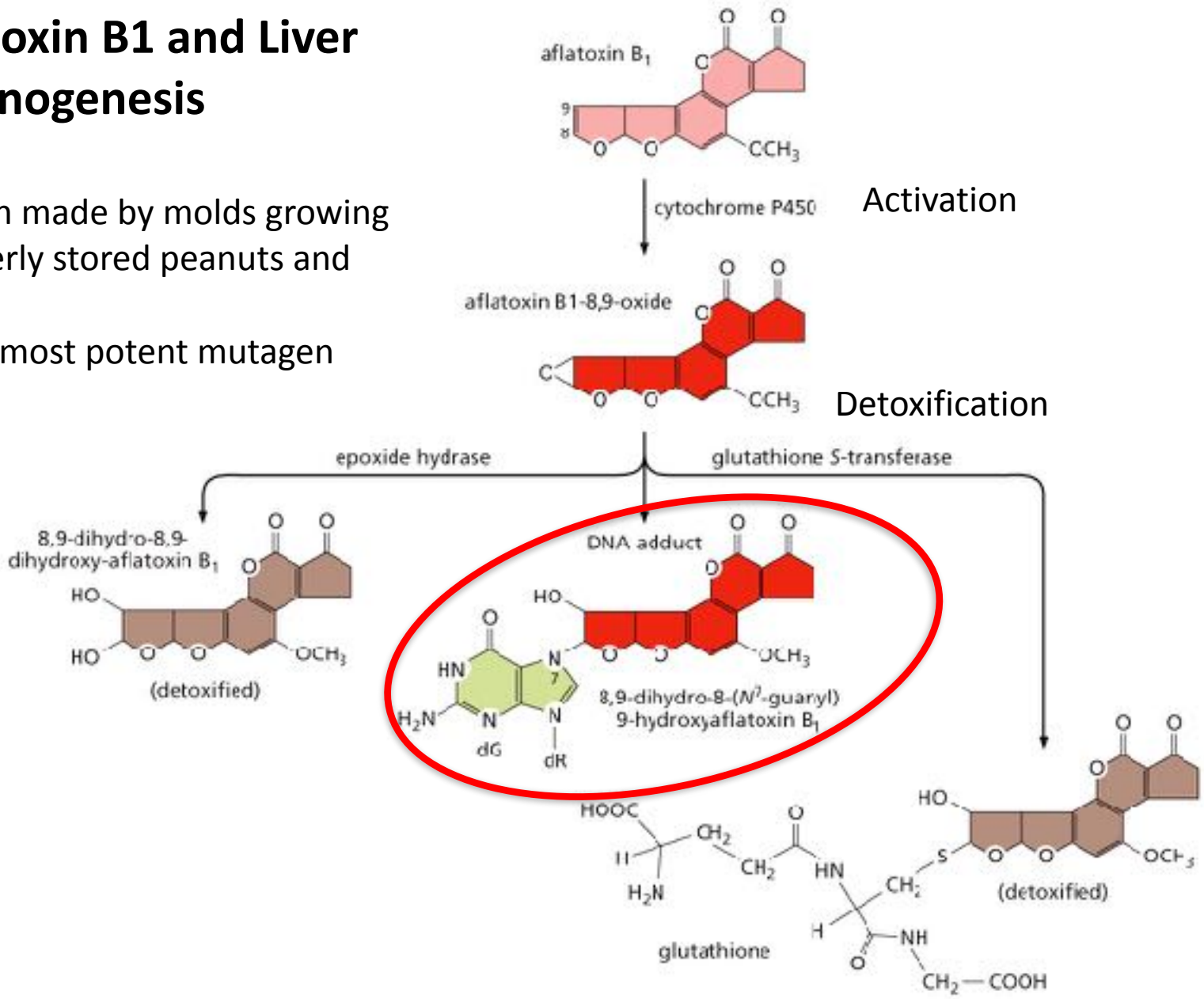
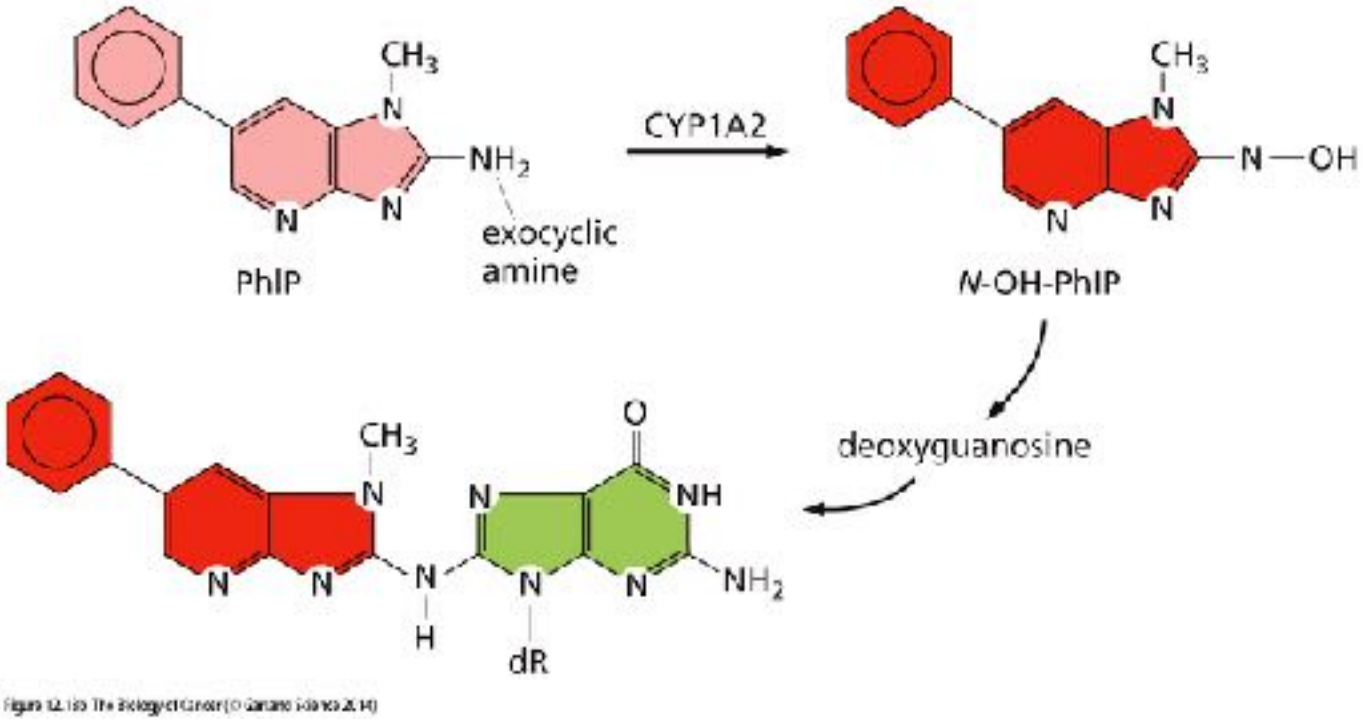


Figure 12.17b The Biology of Cancer (© Garland Science 2014)

Heterocyclic Amines

Heterocyclic amines arise from cooking foods specially red meats at high temperatures.
PhIP is estimated to constitute 2/3rds of the total dietary intake of heterocyclic amines among Americans.
The oxidation of exocyclic amine of PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) by CYP1A2 leads to highly reactive N-OH-PhIP which can DNA adducts.



Oxidation of Bases in the DNA as result of the actions of ROS can be mutagenic in the absence of subsequent DNA repair reactions

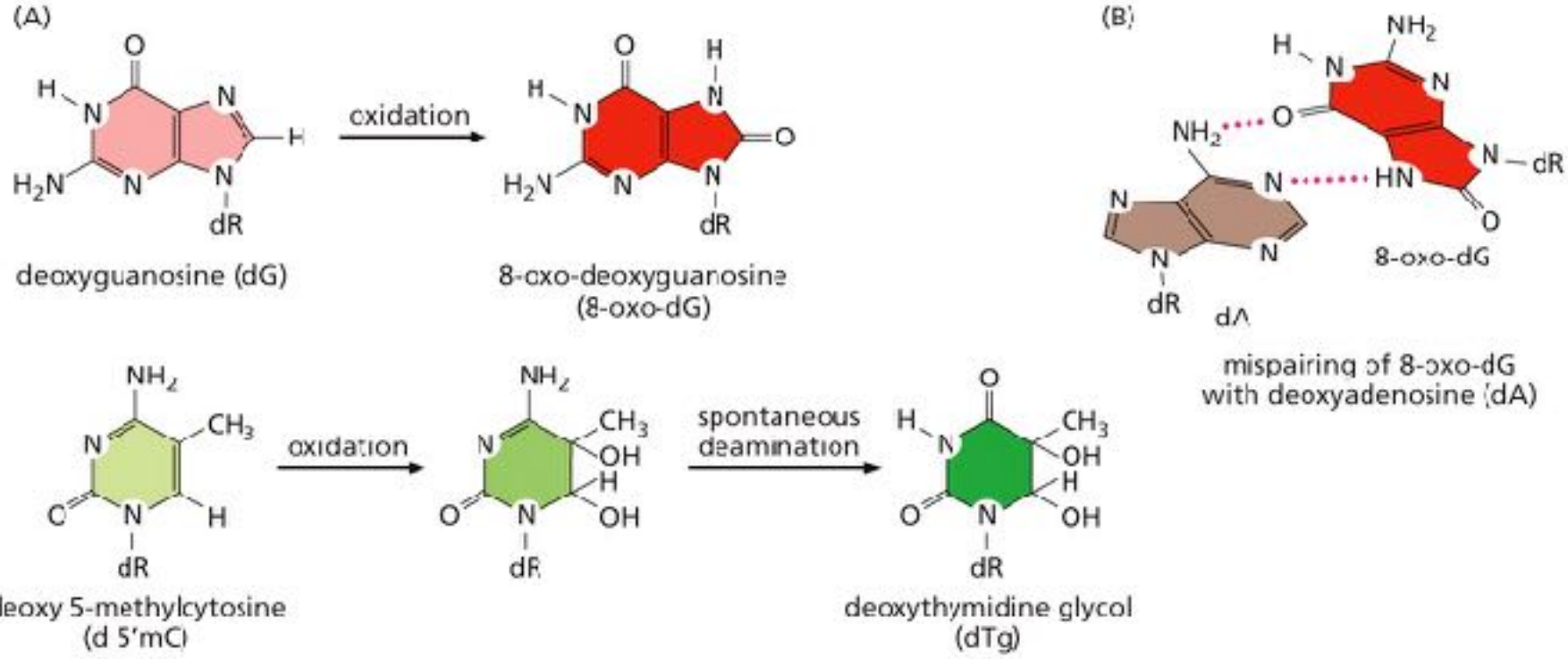


Figure 12.10 The Biology of Cancer (© Garland Science 2014)

Depurination and base deamination

Spontaneous depurination frequently affects guanine within DNA

The deamination reactions affecting purine and pyrimidine bases, lead to changes in nucleotide sequences unless they are repaired.

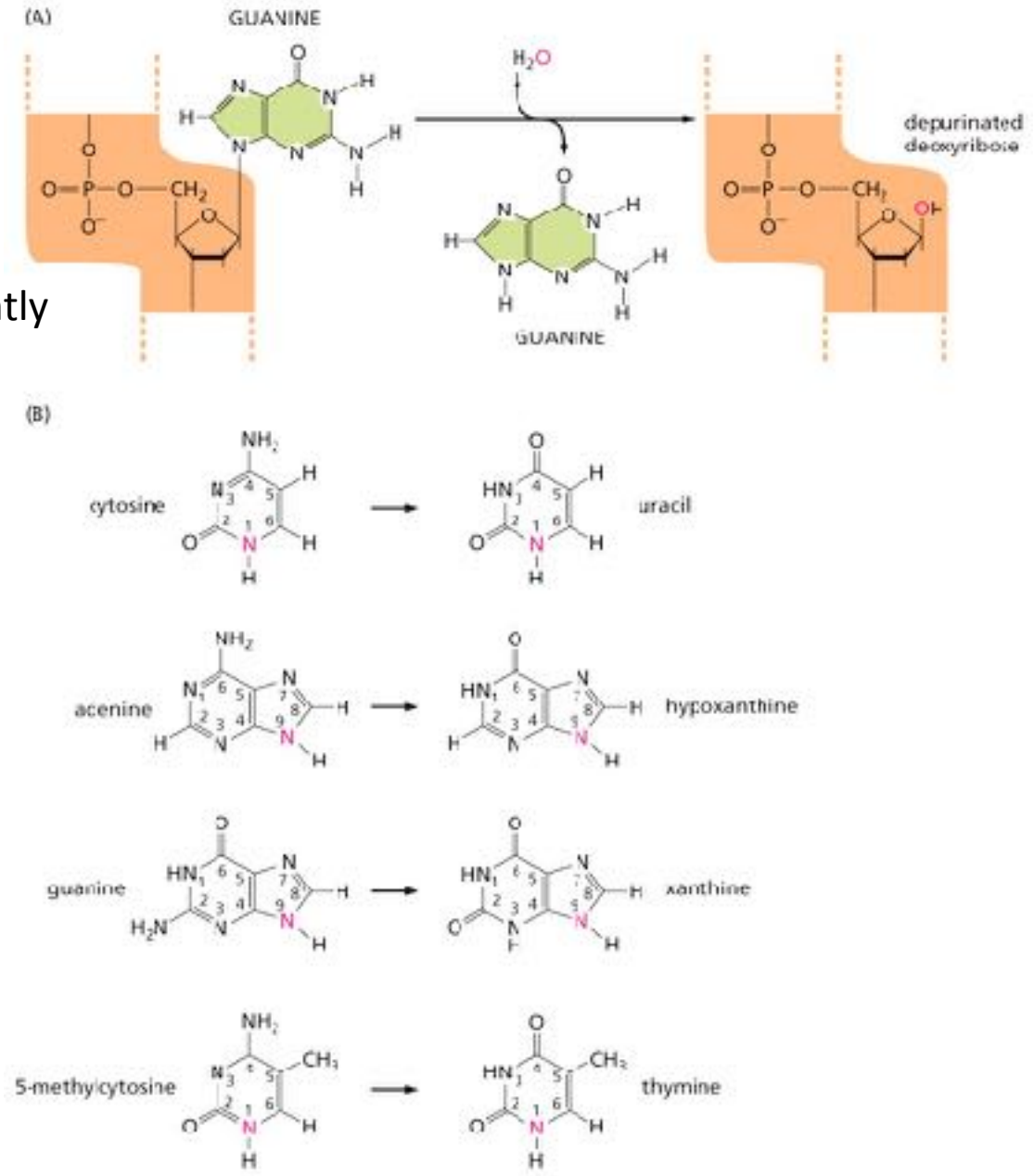
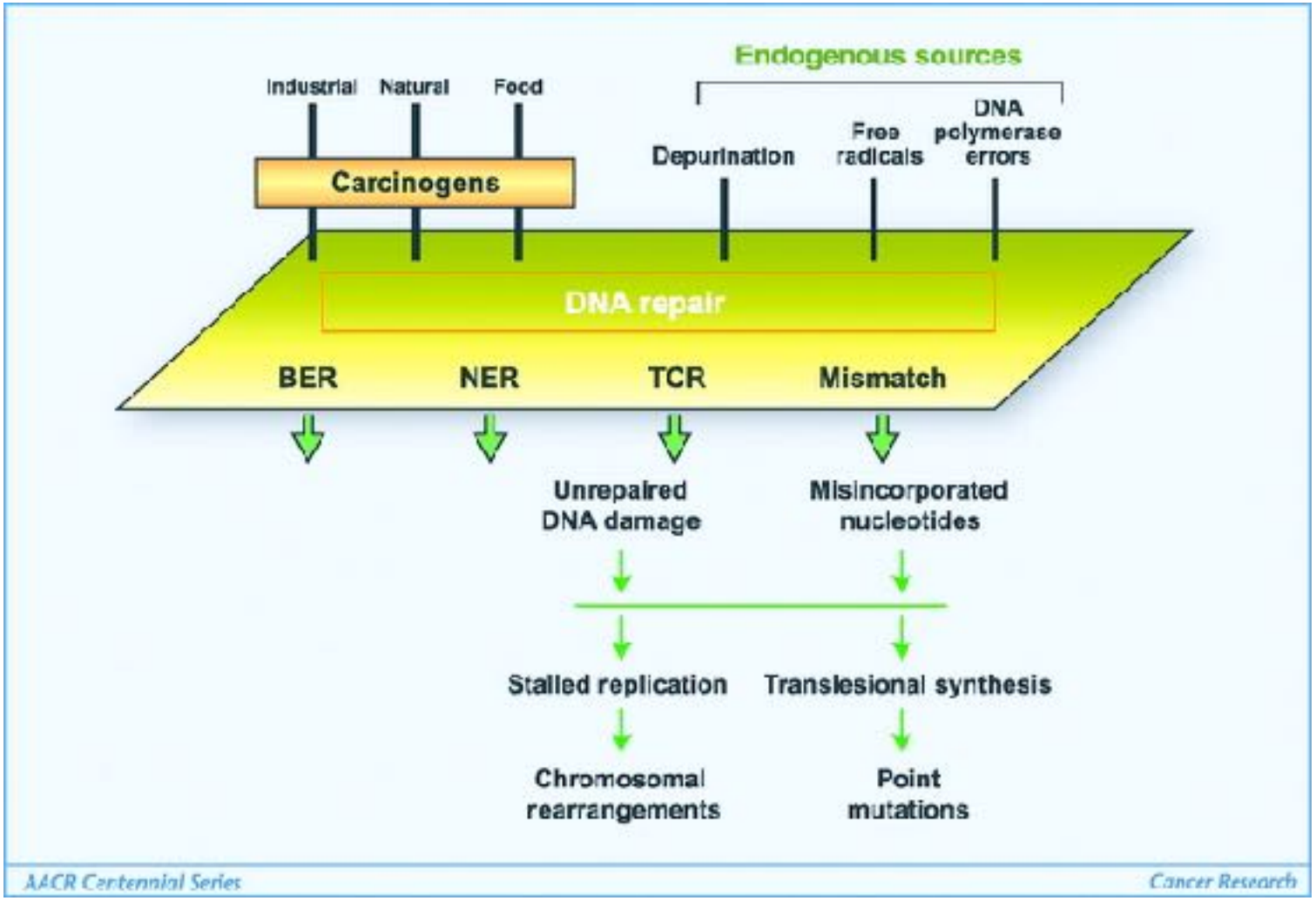


Figure 12.9 The Biology of Cancer (© Garland Science 2014)

• A substance that is not itself a carcinogen can sometimes be turned into carcinogen.
• Pro-carcinogens are activation dependent.
• These compounds require cellular enzymatic metabolism into an ultimate carcinogen in order to exert their carcinogenic action.
• The resulting chemicals can be just as carcinogenic as direct carcinogens.
• Metabolism represents the organism's attempts to detoxify exogenous chemicals to water soluble conjugates which can be excreted.
• But through the detoxifying process a chemical may be activated to an ultimate carcinogenic form.
• These pathways may be modulated by drugs, age, nutrition, hormones or genetics.

Mutations Result from Incomplete DNA Repair.



Loeb L A , and Harris C C Cancer Res 2008;68:6863-6872

Protocol for inducing skin carcinomas in mice

The induction of skin carcinomas by painting carcinogens on the backs of mice requires certain combinations of treatments with initiators and promoters.
Example of initiator :TPA/PMA (12-O-tetradecanoylphorbol-13-acetate)
Example of promoter : DMBA (Dimethylbenz[a]anthracene)

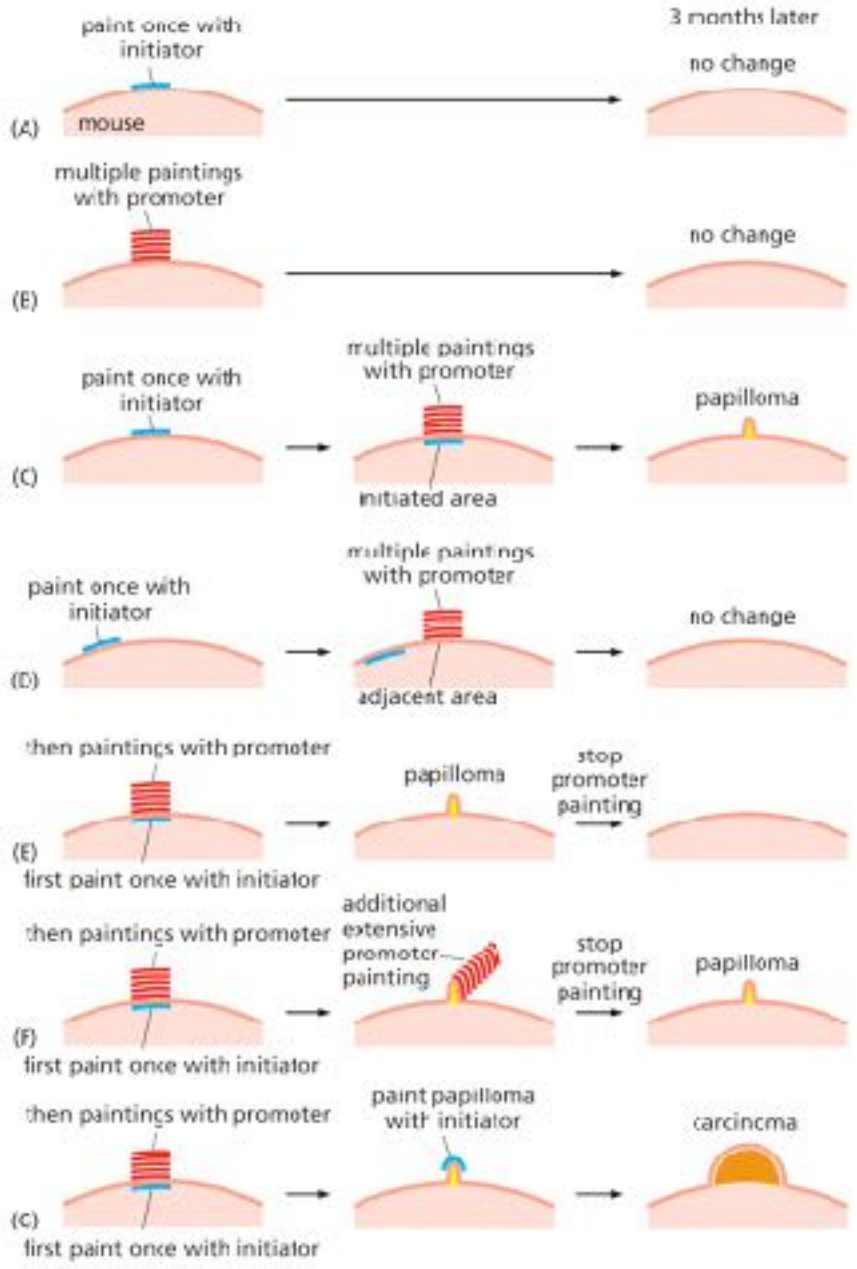


Figure 11.3 The Biology of Cancer (© Garland Science 2014)

Scheme of initiation and promotion of epidermal carcinomas in mice

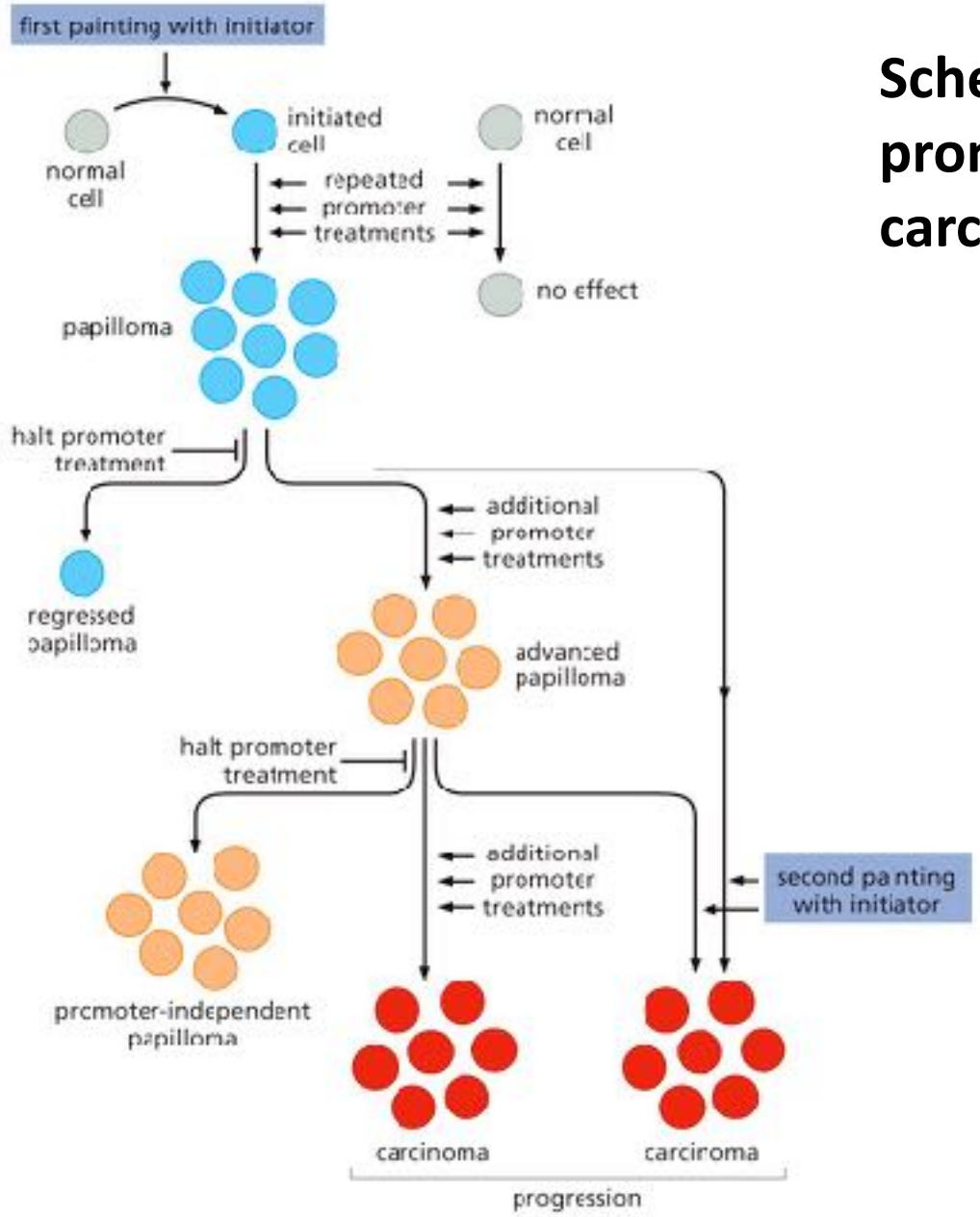


Figure 11.31 The Biology of Cancer (© Garland Science 2014)

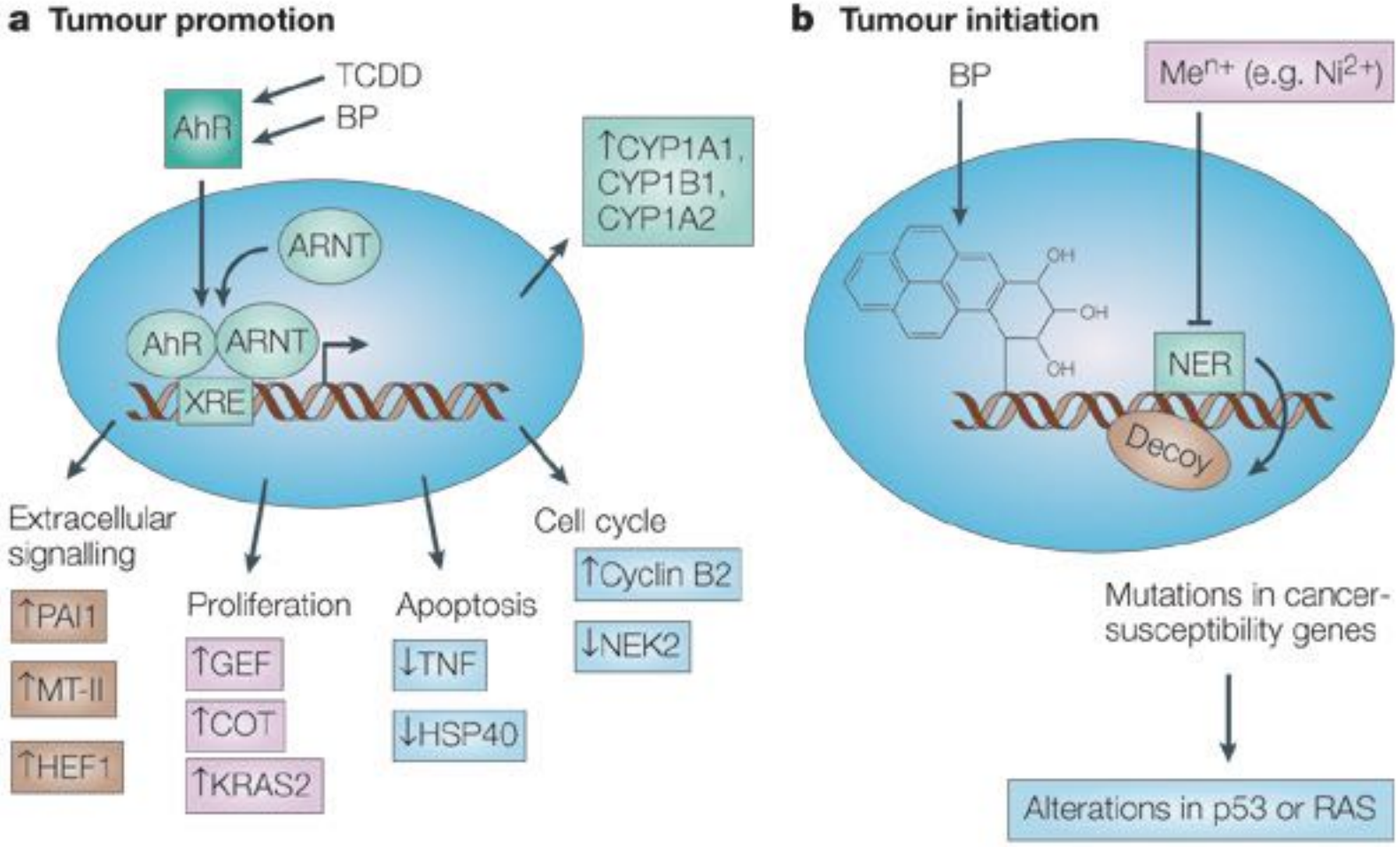

a Tumour promotion
TCDD
BP
AhR
ARNT
AhR
ARNT
XRE
↑CYP1A1,
CYP1B1,
CYP1A2
Extracellular signalling
↑PAI1
↑MT-II
↑HEF1
Proliferation
↑GEF
↑COT
↑KRAS2
Apoptosis
↓TNF
↓HSP40
Cell cycle
↑Cyclin B2
↓NEK2
b Tumour initiation
BP
Me^n+ (e.g. Ni^2+)
OH
OH
OH
NER
Decoy
Mutations in cancer-susceptibility genes
Alterations in p53 or RAS

Table 11.3 Inflammatory conditions and tumor development

Human tumor	Inflammatory condition or inflammation-provoking agent
Bladder carcinoma	schistosomiasis, chronic cystitis
Gastric carcinoma	*H. pylori*–induced gastritis
Hepatocellular carcinoma	hepatitis B/C virus
Bronchial carcinoma	silica
Mesothelioma	asbestos
Ovarian carcinoma	endometriosis
Colorectal carcinoma	inflammatory bowel disease
Esophageal carcinoma	chronic acid reflux
Papillary thyroid carcinoma	thyroiditis
Prostate carcinoma	prostatitis
Lung carcinoma	chronic bronchitis
Gallbladder carcinoma	chronic cholecystitis
Squamous cell skin carcinoma	chronic osteomyelitis

Adapted from F. Balkwill, K.A. Charles and A. Mantovani, *Cancer Cell* 7:211–217, 2005.

Table 11.4 Links between inflammation and cancer pathogenesis

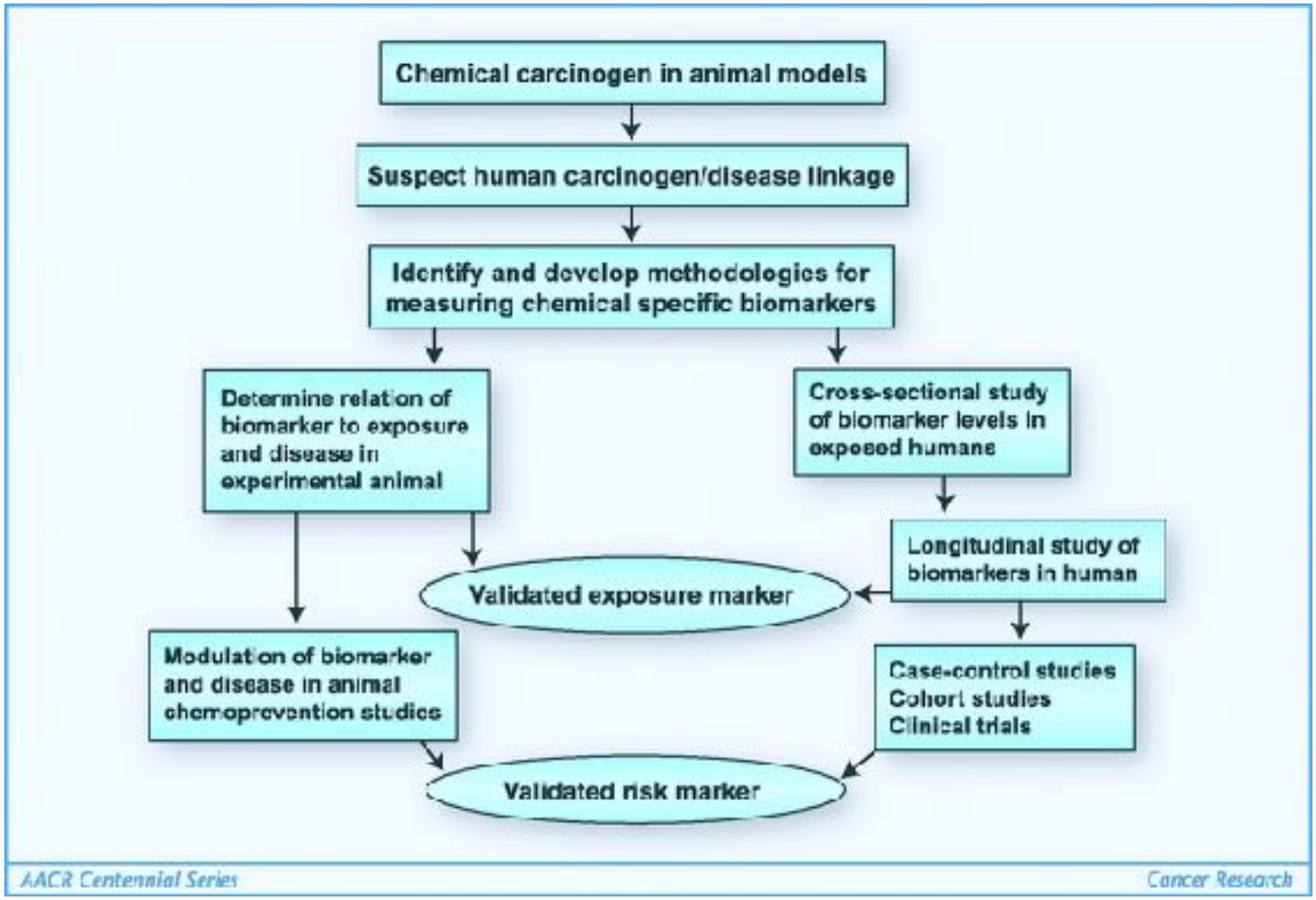
Many inflammatory conditions predispose to cancer
Cancers arise at sites of chronic inflammation
Functional polymorphisms of cytokine genes are associated with cancer susceptibility and severity
Distinct populations of inflammatory cells are detected in many cancers
Extent of tumor-associated macrophage infiltrate correlates with prognosis
Inflammatory cytokines are detected in many cancers; high levels are associated with poor prognosis
Chemokines are detected in many cancers; they are associated with inflammatory infiltrate and cell motility
Deletion of cytokines and chemokines protects against carcinogens, experimental metastases, and lymphoproliferative syndrome
Inflammatory cytokines are implicated in the action of nongenotoxic liver carcinogens
The inflammatory cytokine tumor necrosis factor is directly transforming *in vitro*
Long-term NSAID use decreases mortality from colorectal cancer

Courtesy of F. Balkwill. From F. Balkwill and A. Mantovani, *Lancet* 357:539–545, 2001.

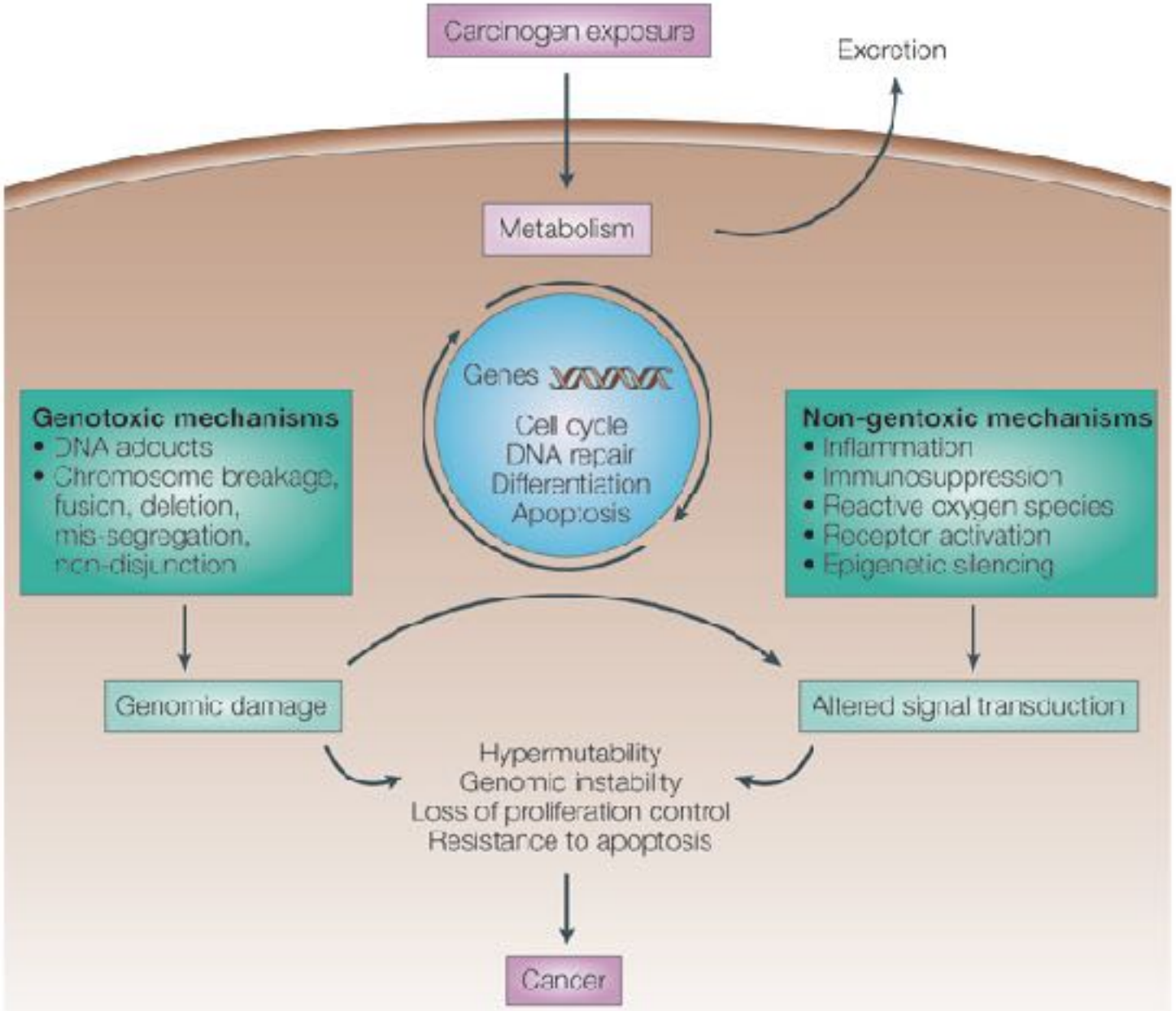
Known or suspected human tumor promoters and their sites of action

Agent or process	Cancer site
Hormones	
Estrogen	endometrium
Estrogen and progesterone	breast
Ovulation	ovary
Testosterone	prostate
Drugs	
Oral contraceptives, anabolic steroids	liver
Analgesics	renal pelvis
Diuretics	kidney
Infectious agents	
Hepatitis B/C viruses	liver
Schistosoma haematobium blood fluke	bladder
Schistosoma japonicum—blood fluke	colon
Clonorchis sinensis—liver fluke	biliary tract
Helicobacter pylori—bacterium	stomach
Malarial parasites	B cell
Tuberculosis bacillus	lung
Chemical agents	
Betel nut, lime	oral cavity
Chewing tobacco	oral cavity
Bile	small intestine
Salt	stomach
Acid reflux	esophagus
Physical or mechanical trauma	
Asbestos	mesothelium, lu
Gallstones	gallbladder
Coarsely ground corn	stomach
Head injury	meninges
Chronic irritation/inflammation	
Tropical ulcers[a]	skin
Chronic ulcerative colitis	colon
Chronic cystitis	bladder
Chronic pancreatitis	pancreas

A modified molecular epidemiologic approach for validating causal relationships between carcinogen exposure and cancer risk.



Loeb L A , and Harris C C Cancer Res 2008;68:6863-6872


Carcinogen exposure
Excretion
Metabolism
Genes
Cell cycle
DNA repair
Differentiation
Apoptosis
Genotoxic mechanisms
• DNA adducts
• Chromosome breakage, fusion, deletion, mis-segregation, non-disjunction
Non-genotoxic mechanisms
• Inflammation
• Immunosuppression
• Reactive oxygen species
• Receptor activation
• Epigenetic silencing
Genomic damage
Altered signal transduction
Hypermutability
Genomic instability
Loss of proliferation control
Resistance to apoptosis
Cancer

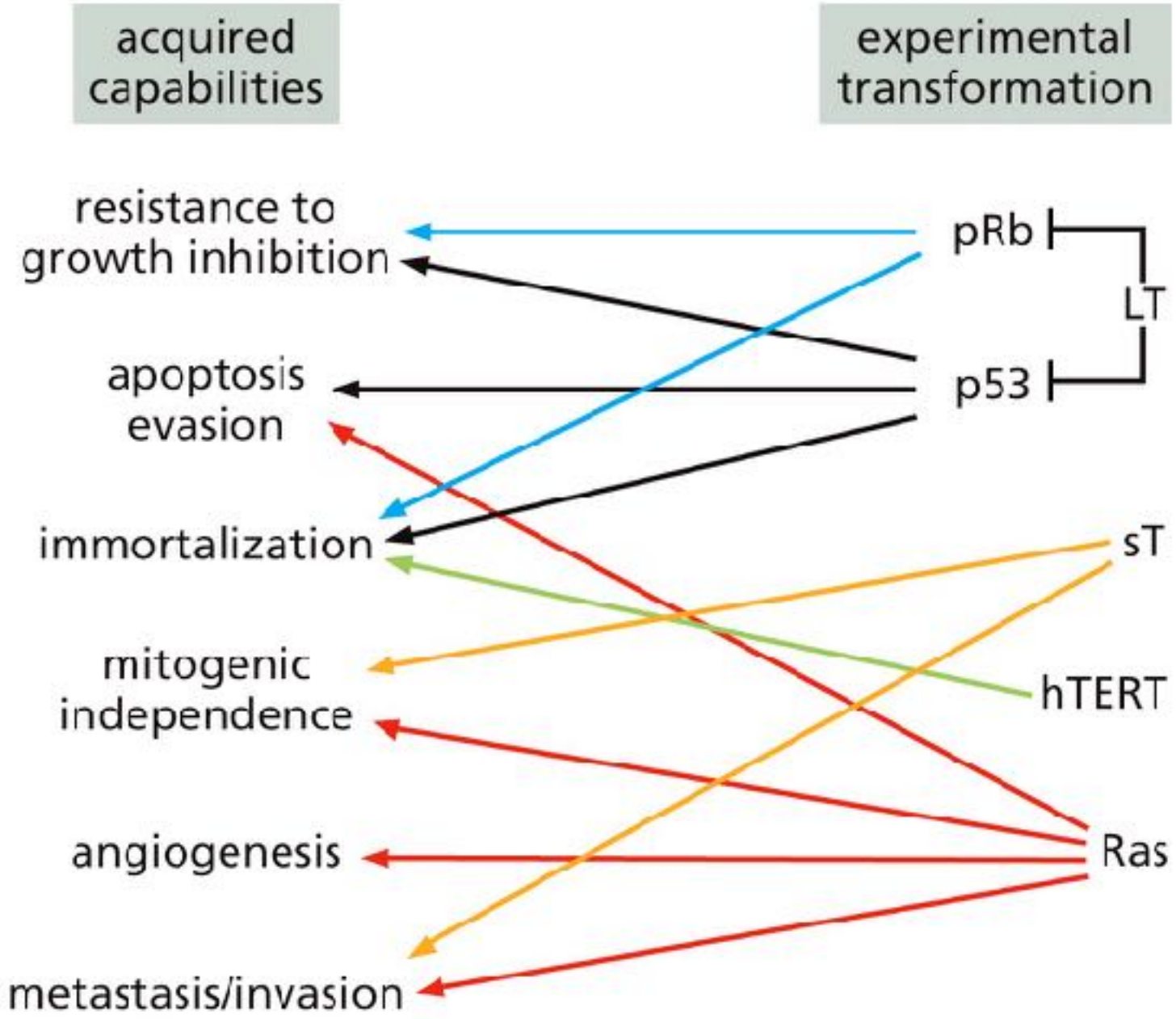


Figure 11.44 The Biology of Cancer (© Garland Science 2014)

Table 2.9 Examples of etiologic mysteries: epidemiologic correlations between environmental/lifestyle factors and cancer incidence that lack a clear explanation of causal mechanism[a]

Lifestyle, dietary factor, or medical condition	Altered cancer risk
High birth weight	premenopausal breast cancer ↑ infant acute leukemia ↑
Processed red meat[b]	ER+ breast cancer ↑ squamous cell and adenocarcinoma of lung ↑
Childhood soy consumption	breast cancer ↓
Well-done red meat	prostate cancer ↑
Western diet—high in fat, high in red meat	colorectal, esophageal, liver, and lung cancer ↑
Exercise	hormone-responsive breast cancer ↓
Diet with cruciferous vegetables	prostate cancer ↓
High body-mass index (BMI)	multiple cancer types ↑
Higher ratio of number of daughters to number of sons born to a woman	ovarian carcinoma ↑
Parkinson's disease	melanoma ↑
Low circulating vitamin D	breast cancer incidence, CRC mortality ↑
Periodontal disease	esophageal carcinoma ↑
Coffee consumption	hepatocellular carcinoma ↓

Further Reading:

1. The Biology of Cancer by Robert A. Weinberg. Parts of Chapters 2 and 11.

2. Advances in chemical carcinogenesis: a historical review and prospective. Loeb LA, Harris CC.Cancer Res. 2008 Sep 1;68(17):6863-72.

3. Nature and nurture - lessons from chemical carcinogenesis.Luch A.Nat Rev Cancer. 2005 Feb;5(2):113-25.

4. The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis.Nebert DW, Dalton TP.Nat Rev Cancer. 2006 Dec;6(12): 947-60.

5. Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment.Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, Starr TB.Toxicol Sci. 2011 Mar;120 Suppl 1:S130-45.

6. Basic properties and molecular mechanisms of exogenous chemical carcinogens.Irigaray P, Belpomme D.Carcinogenesis. 2010 Feb;31(2):135-48.