Genetic mechanisms in the etiopathogenesis of sporadic and familial cancers

MED 213

The Genetic Bases of Cancer

Oncogenes
Tumor suppressor genes
Repair genes

Environmental mutagens
(biological, chemical, physical agents)

Genetic mechanisms in etiopathogenesis of sporadic and familial cancers

Pathways in Carcinogenesis

Epigenetics and Cancer

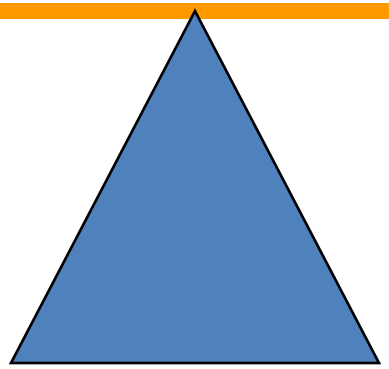
Molecular targets for Cancer Therapy

The Cancer Genetics

- Cancer is caused by genetic alterations
- Genetic alterations can be inherited and/or acquired
- Progression is clonal, initiates in an individual cell
- Carcinogenesis is a process that alters the genomic stability and functionality of the cell
- Especially related to cell proliferation mechanisms
- Genetic alterations build up by time
- Positive correlation between age and incidence
- Individuals may be susceptible to cancer formation
- These susceptibilities form the bases of both familial and heritable cancer cases

Proliferation

Cell Death



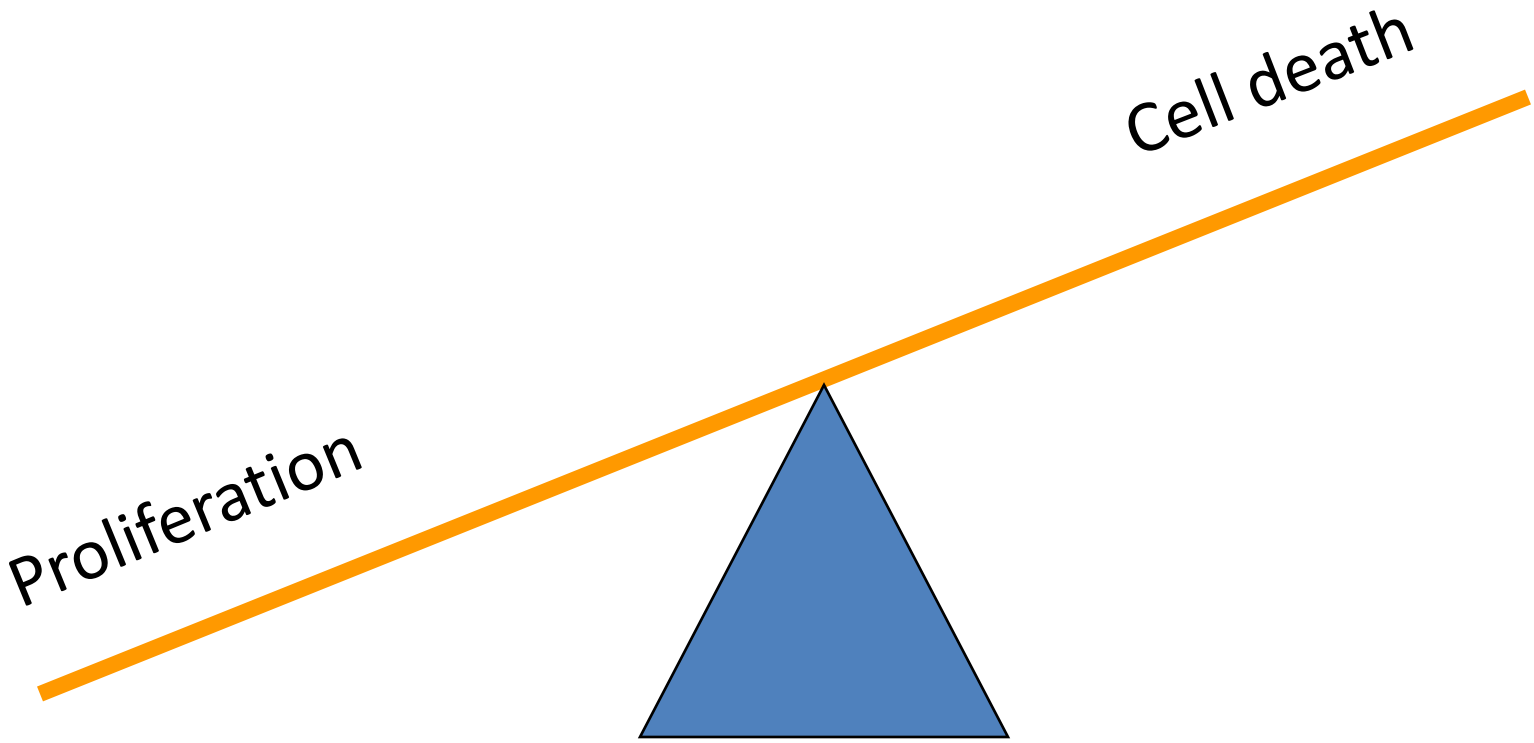
Cell cycle control

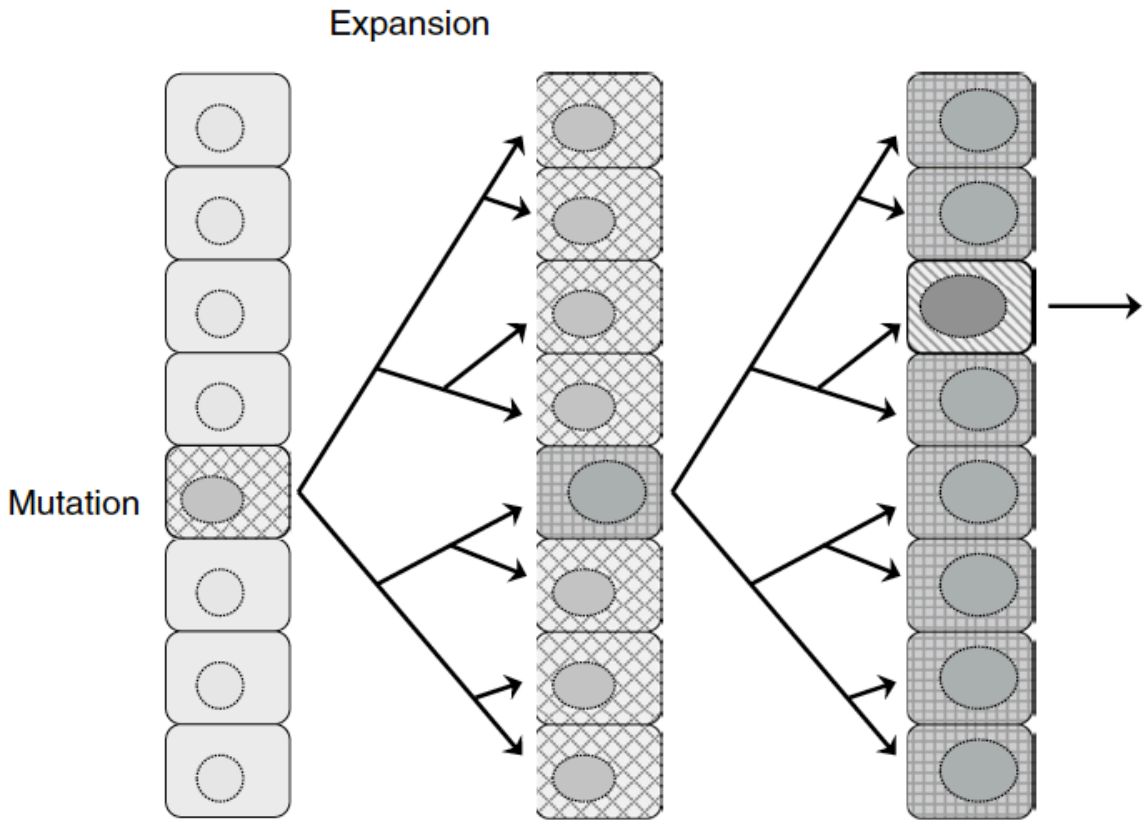
Proto-onkogenes
Telomerases
Oncomirs

Apoptosis

Tumor suppressor genes
Oncomirs

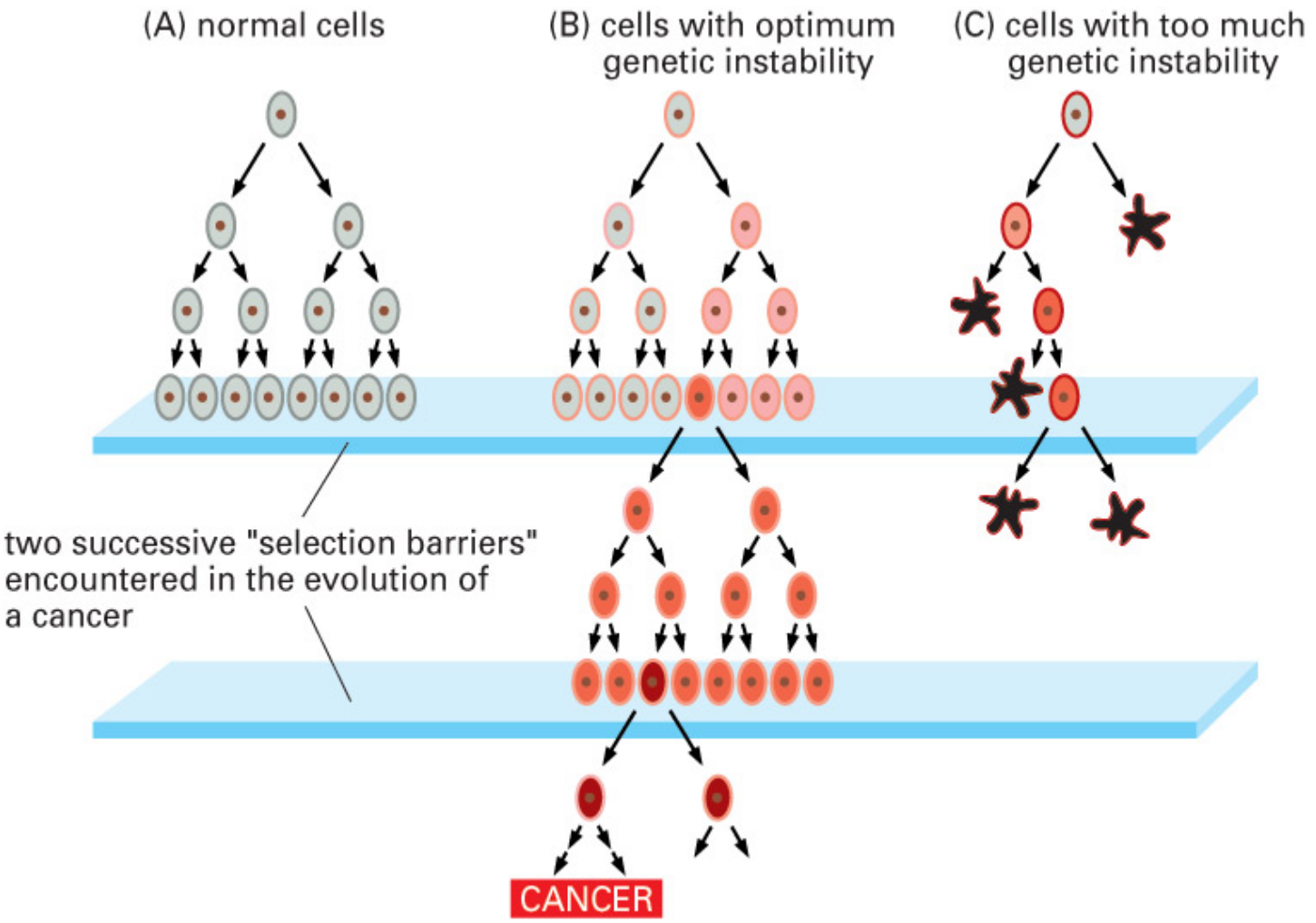
Neoplasia /Carcinogenesis

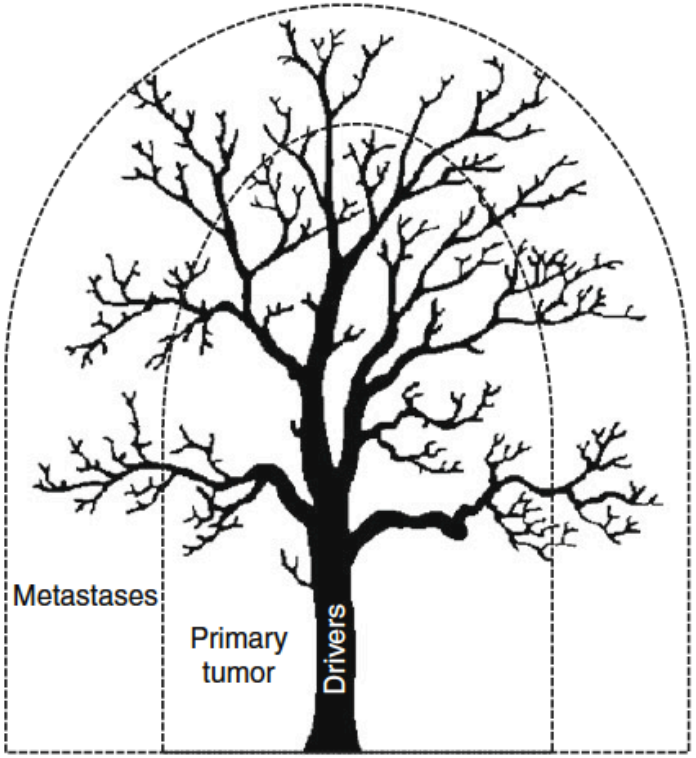




Clonal evolution of a neoplasm.
A single cell in a normal tissue acquires an alteration that confers a growth advantage.
That cell divides and thus expands over time into a distinct clone.
A cell within that clone acquires a second mutation that provides an additional growth advantage.
A tumor results from iterative rounds of mutation and clonal expansion.

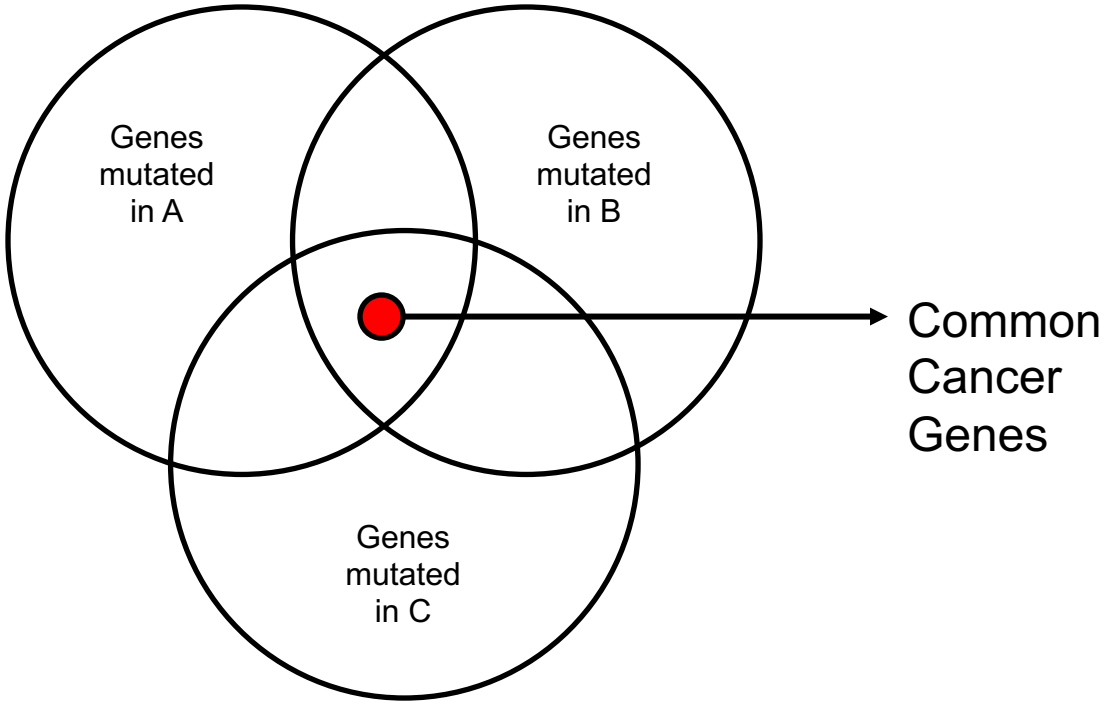
Tumor formation requires optimum genetic stability of the cell





Tumor heterogeneity

- Cancers evolve from a clonal population of proliferative cells that becomes increasingly more genetically heterogeneous with each successive generation.
- Drivers feed the growth of every part of the tree. The branches are somatic mutations that arise later, as a product of cell division, define distinct subpopulations within the tumor.
- The majority of these mutations are passengers. Metastases develop from founder cells that differ substantially from one another, and therefore exhibit a large degree of intermetastatic genetic heterogeneity.

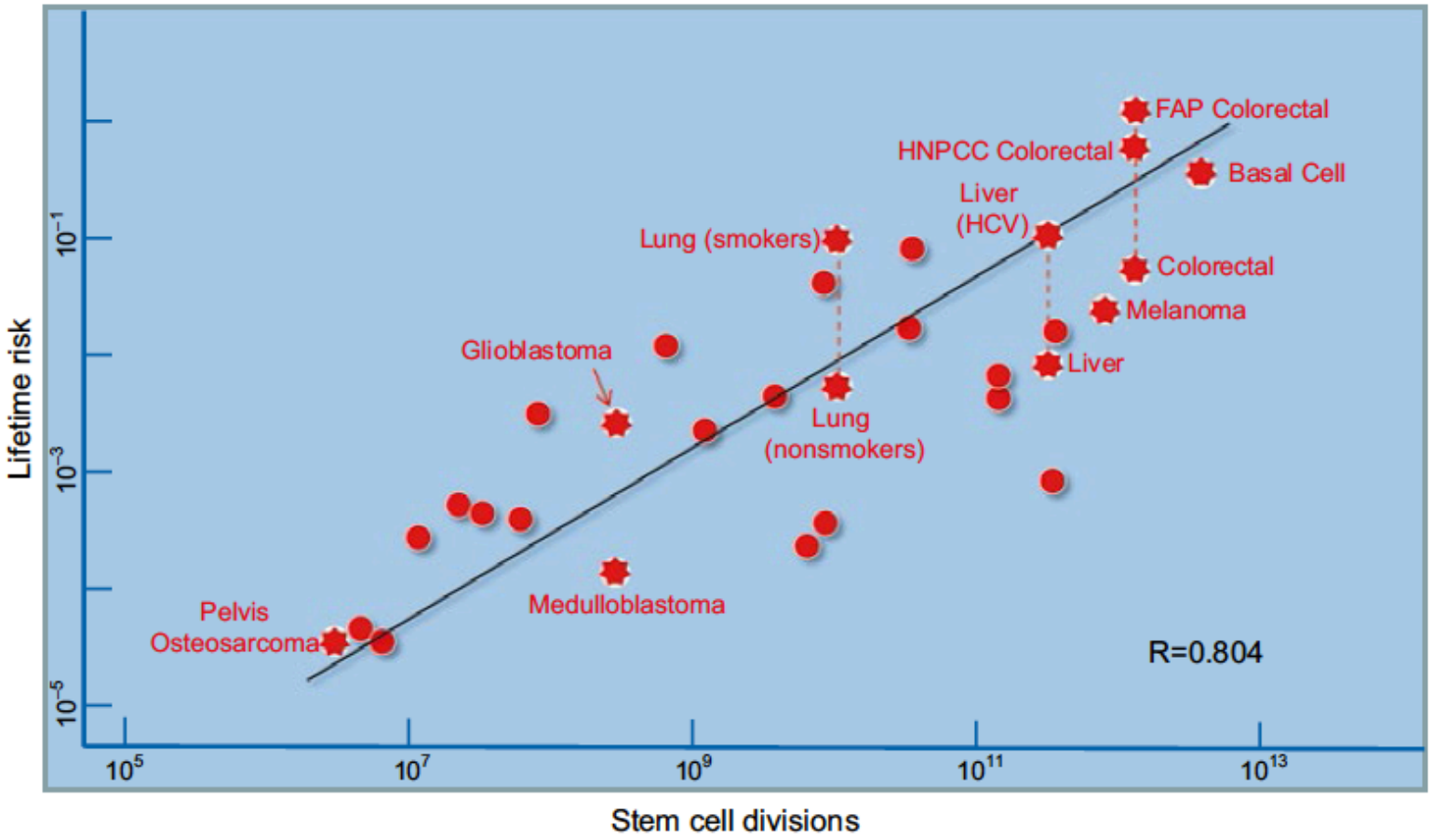


Common and unique drivers of cancers from the same tissue:

The driver mutations found in cancers are diverse and often tissue-specific.

In this example, comparison of the set of genes mutated in tumors A, B and C shows that some driver mutations are unique to each tumor in which they occur, but there is also significant overlap.

A proportion of mutated genes are common to all three tumors;
these represent highly prevalent cancer genes



Cancers arise more frequently in tissues that are highly proliferative.

The lifetime risk of cancer in any given tissue is positively correlated with the total number of stem cell divisions that occur in that tissue.

The linearity of this relationship (R close to 1) supports a large role for replicative mutations in human cancers.

This study examined 31 types of cancer, from diverse tissues.

Common tumors of the breast and prostate were excluded from this analysis because of uncertainty in the absolute number of stem cells in these tissues.

INCREASE of CANCER INCIDENCE BY AGE

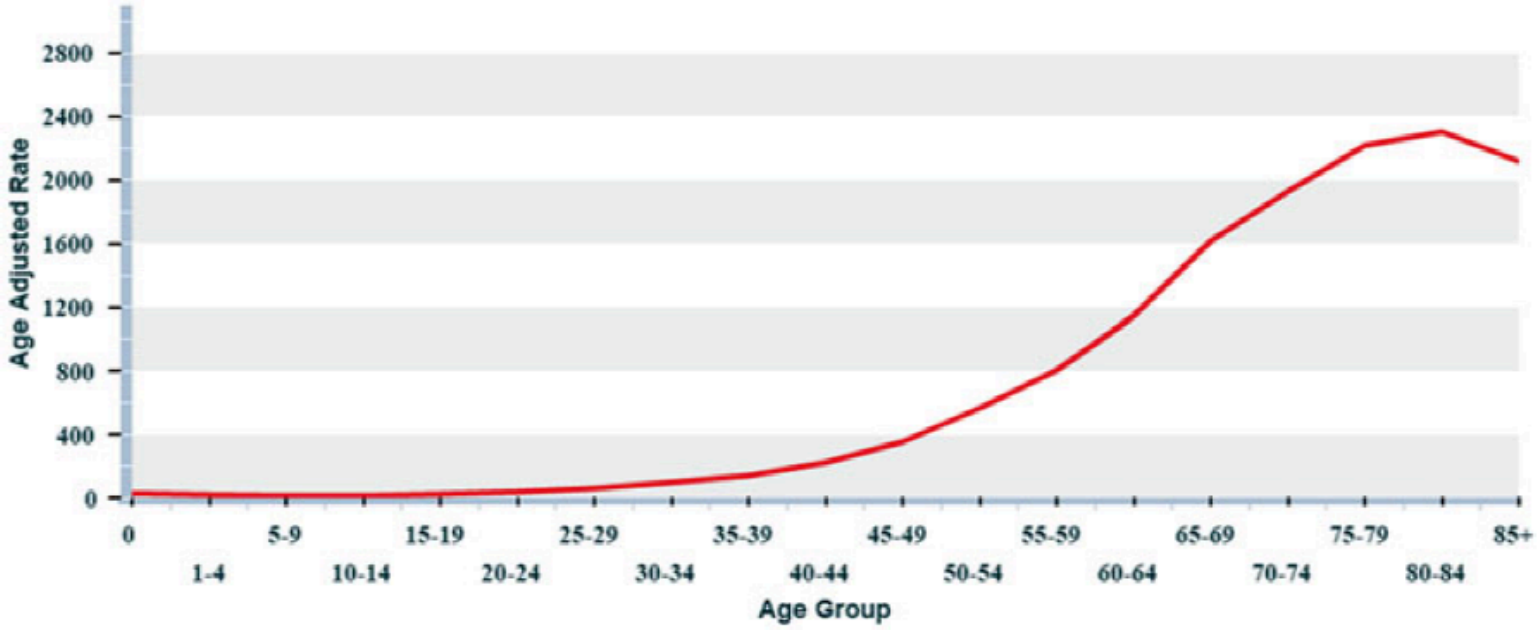


Fig. 5.2 Cancer incidence, by age group. The overall incidence of cancer at all sites rises with increasing age and peaks around age 80. Incidence rates include both sexes and all races, are per 100,000 and are from surveys dating from 1975 to 2012, age-adjusted to the 2000 US population. Primary data are from the Surveillance, Epidemiology and End results program (SEER), of the National Cancer Institute

Progression of carcinogenesis from zygote to somatic cells

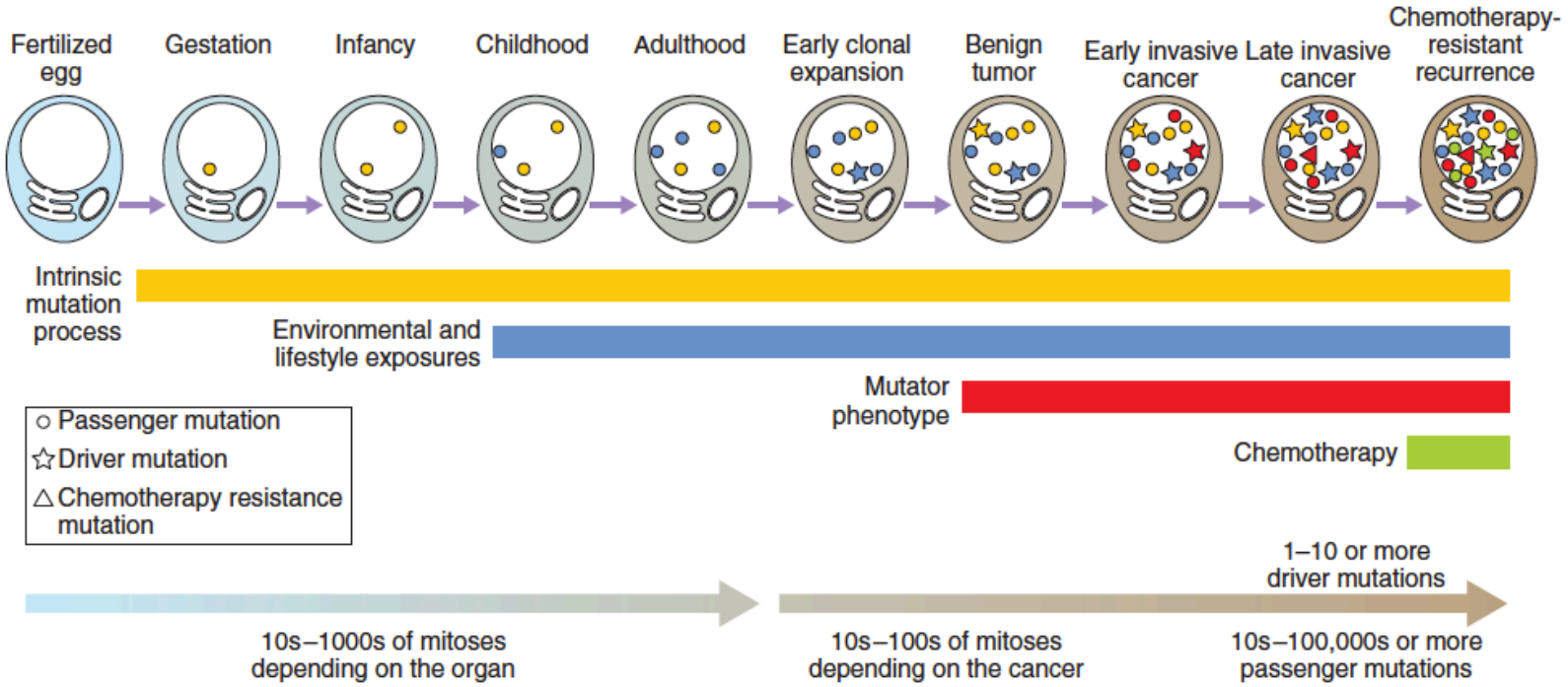
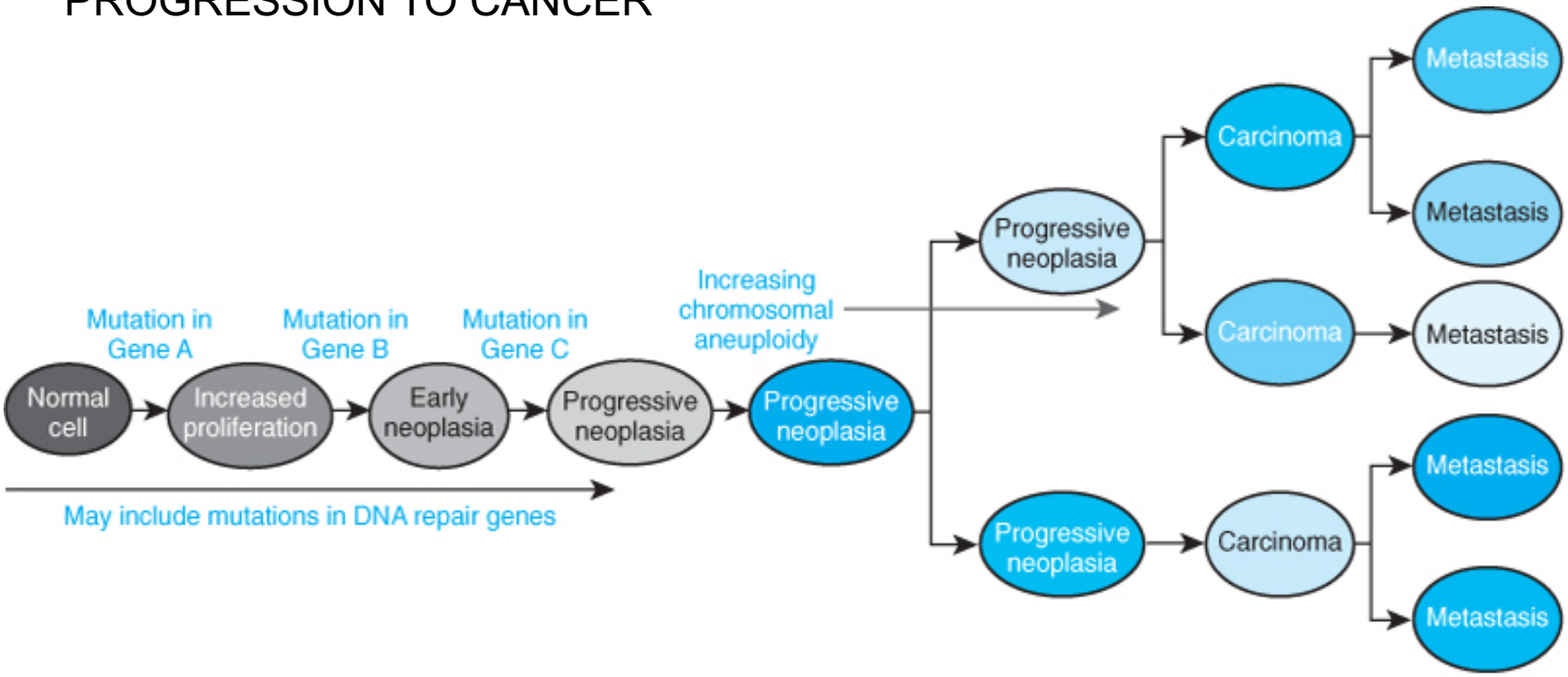
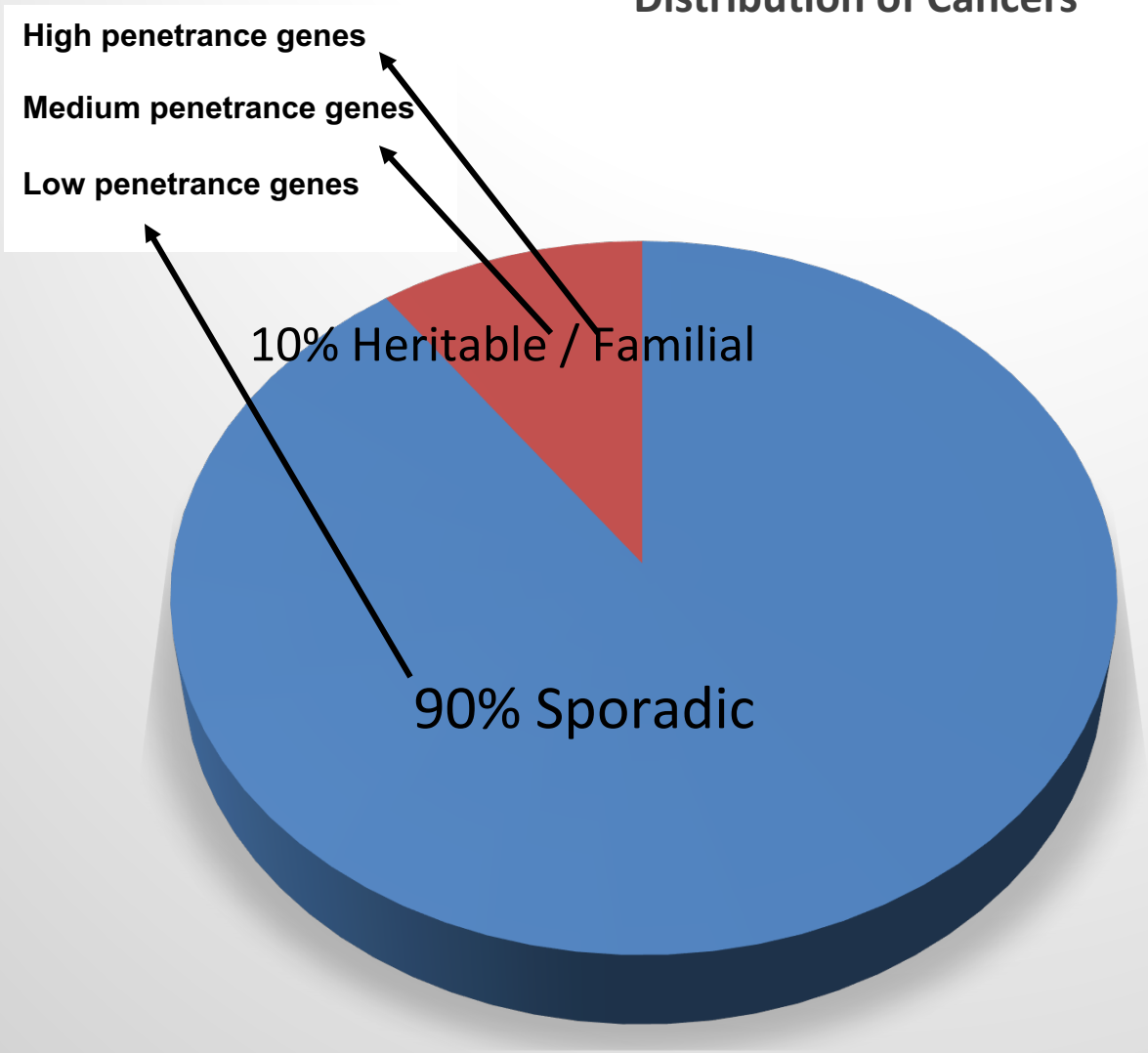


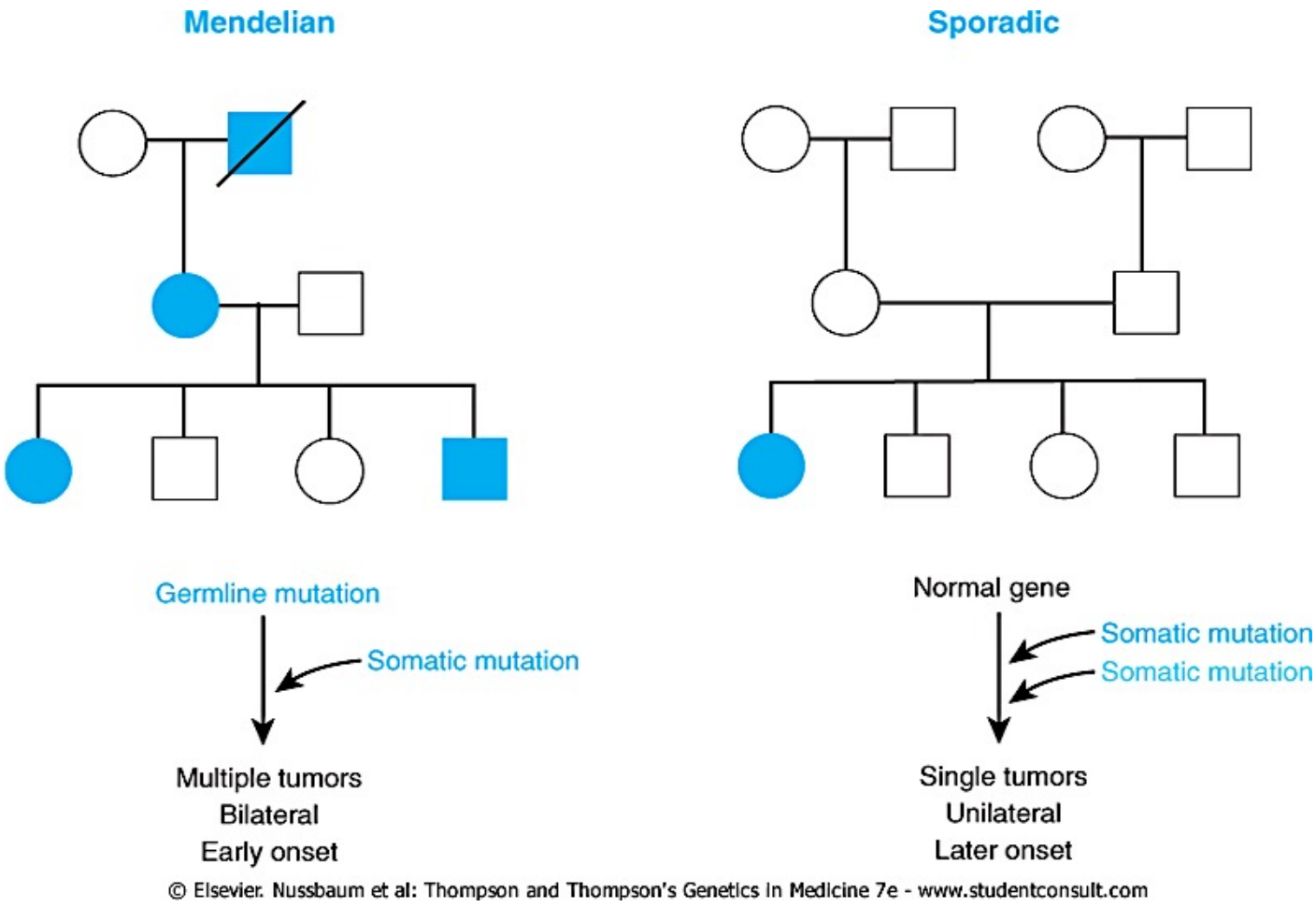
FIGURE 14.1 The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them. Mutations may be acquired through both intrinsic cell division processes and as a result of mutagens. DNA repair defects may contribute, but driver mutations will cause clonal expansion, with passenger mutations having little overall effect. Relapse following chemotherapy may be due to resistant mutations predating treatment. *(Reproduced with permission from Stratton MR, Campbell PJ, Futreal PA 2009 The cancer genome. Nature 458:719–24.)*

PROGRESSION TO CANCER



Distribution of Cancers





Syndrome	*MIM#* [a]	*Gene(s)*	*Population incidence*	*Penetrance*[b]
Ataxia-telangiectasia	208900	*ATM*	1/30 000 to 1/100 000	100%
Birt–Hogg–Dube	135150	*BHD*	Unknown, rare	Unknown, but reduced
Bloom syndrome	210900	*BLM*	Unknown, rare	100%
Carney complex	160980	*PRKRA1A*	Rare	Unknown
Cowden syndrome	**158350**	***PTEN***	**1/200 000**	**90–95%**
Familial adenomatous polyposis	**175100**	***APC***	**1/5000 to 1/10 000**	**100%**
Familial malignant melanoma	155600	*CDKN2A (TP16), CMM1, CDK4*	Unknown	100%
Familial paraganglioma syndrome	168000, 185470	*SDHD, SDHB*	Rare	Unknown
Fanconi anaemia	227650	*FANCA, FANCB, FANCC, FANCD, FANCE, FANCF, FANCG, FANCL*	1/360 000	100%
Hereditary breast–ovarian cancer syndrome	**113705, 600185**	***BRCA1 and BRCA2***	**1/500 to 1/1000**	**Up to 85%**
Hereditary diffuse gastric cancer	137215	*CDH1*	Unknown, rare	90%
Hereditary leiomyomatosis and renal cell carcinoma	605839	*FH*	Unknown, rare	Unknown, but reduced
Hereditary nonpolyposis colon cancer	**114500**	***MLH1, MSH2, MSH6, PMS1, PMS2***	**1 in 400**	**90%**
Hereditary papillary renal cell carcinoma	605074	*MET*	Unknown	Unknown, but reduced
Hyperparathyroidism–jaw tumour syndrome	145001	*HPRT2*	Unknown, rare	90%
Juvenile polyposis syndrome	**174900**	***MADH4 (SMAD4), BMPR1A***	**1/100 000**	**90–100%**

and renal cell carcinoma				
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Li–Fraumeni syndrome	**151623**	***TP53***	**Rare**	**90–95%**
Multiple endocrine neoplasia type 1	**131100**	***MEN1***	**1/100 000**	**95%**
Multiple endocrine neoplasia type 2	**171400, 162300**	***RET***	**1/30 000**	**70–100%[c]**
Neurofibromatosis type 1	162200	*NF1*	1/3000	100%
Neurofibromatosis type 2	101000	*NF2*	1/40 000	100%
Nevoid basal cell carcinoma syndrome	109400	*PTC*	1/57 000	90%
Nijmegen breakage syndrome	251260	*NBS1*	Rare	100%
Peutz–Jeghers syndrome (PJS)	**175200**	***LKB1 (STK11)***	**1/200 000**	**95–100%**
Retinoblastoma, hereditary (RB)	180200	*RB*	1/13 500 to 1/25 000	90%
Rothmund–Thomson syndrome	268400	*RECQL4*	Rare	100%
Tuberous sclerosis (TS)	191100, 191092	*TSC1, TSC2*	1/30 000	95–100%
von Hippel–Lindau (VHL)	**193300**	***VHL***	**1/36 000**	**90–95%**
Xeroderma pigmentosum	278700, 133510, 278720, 278730, 278740, 278760, 278780	*XPA, ERCC3, XPC, ERCC2, XPE, ERCC4, ERCC5*	1/1 000 000[d]	100%

Indications of familial or inherited cancers:

- Two or more individuals in a family with same type of cancer
- Early onset cancer diagnosis in a family with multiple cases
- Same individual with more than one primary tumors
- Bilateral (symmetric organs) Existance of
- Existance of cases related to familial/inherited cancer syndromes
- A family with increased incedence of cancer cases relative to general population
- Cancer cases with congenital malformations
- Autosomal dominant inheritance

Pathways effected in Carcinogenesis

Cancer related genes effect the pathways at three basic cellular process

1. Cell fate
2. Cell viability
3. Genomic stability / genome maintenance

Cancer pathways are determined by protein-protein interactions. These lead to four outcomes

1. Structural changes
2. Functional changes
3. Spatial changes
4. Molecule life cycle